The New England
Journal of Medicine

Copyright, 1956, by the Massachusetts Medical Society

Volume 255 DECEMBER 13, 1956 Number 24

LUNG CANCER IN WOMEN*

A Study of Environmental Factors

ERNEST L. WYNDER, M.D.,† IRWIN J. BROSS, PH.D.,‡ JEROME CORNFIELD, B.S.,§ AND WALTER E. O'DONNELL, M.D.¶

NEW YORK, NEW YORK, AND BETHESDA, MARYLAND

ALTHOUGH much has been written about etiologic factors in the development of lung cancer in men during recent years, little has been said about the role of these factors in women. The primary reason for this apparent neglect is the fact that lung cancer is still a rather uncommon disease among women, so that a sufficient number of cases cannot be easily obtained for an epidemiologic survey.

The present study is based on environmental data of proved cases of lung cancer in women, all of which were diagnosed in the period 1953 to 1955. The purpose has been to study the role of factors previously examined for men. Thus, special emphasis was placed on smoking, occupations and residence. We wanted to determine whether the importance of these factors varied not only between the cases of lung cancer and an appropriate set of controls but also between different histologic types. This study also sought to determine whether the widening sex ratio of lung cancer could be accounted for by the degree of duration of exposure to factors suspected of being of etiologic significance in the development of this disease.

Before the results are presented some of the pertinent data in the literature on lung cancer in women are reviewed.

MORTALITY RATES

The mortality from lung cancer in women today is similar to that of men in 1930 (Table 1). The pattern varies by age group, however, so that for older women the mortality in 1950 was equal to that for older men in 1940 (Fig. 1). The mortality from lung cancer in women, which is still relatively low today in all countries where adequate data are reported (varying from 2 to 6 per 100,000),[2] seems to be slightly higher in England (6 in 1950) and Finland (5.1 in 1950) than in other European countries.[2] This is in line with the higher rate in men reported for these two countries. Though the mortality from lung cancer in women is still low it has been subject to a gradual but steady rise in Europe as well as in the United States. In Great Britain, for example, the rate rose from 0.7 per 100,000 (1901-1920) to 2.5 (1930-1939) and to 6.1 in 1951; it rose from 1.6 per 100,000 (1931) to 3.0 (1952) in Canada, from 4.0 (1931) to 5.0 (1950) in Denmark and from 2.1 (1930) to 4.5 (1952) in the United States.

Thus, although there has been a moderate increase in the incidence of lung cancer in women, the rate of increase has been far less dramatic than that for men.

SEX RATIO

One of the most striking points about lung cancer is the predominantly male sex ratio. In the early part of this century the ratio of male to female cases was described as between 1:1 and 3:1. Adler's[3] monograph (1912) gave a sex ratio of 3:1. Walshe,[4] writing in 1898, stated that lung cancer was a very rare disease but occurred about equally in both sexes. The early data from England, as well as from the United States, show a sex ratio of nearly 1:1 in the early part of the century. In Great Britain, where the ratio of male to female deaths from this disease was 5.7 in 1951, it was only 1.9 in 1925 and 1.5 in 1915.[5] In the United States the ratio was 4.9 in 1952 and only 1.7 in 1930.[1] More recently, data show that this sex ratio has widened to between 5:1 and 9:1. It thus becomes a point of particular interest to determine the factor or factors that can account for this changing sex ratio.

HISTOLOGY

Studies of lung cancer in women that present data by histologic type show a greater proportion of adenocarcinomas than similar studies for men. Even recent

*From the Section of Epidemiology, Division of Preventive Medicine, Sloan-Kettering Institute, and the Division of Research Services of the National Institutes of Health.

Supported by a grant from the American Cancer Society.

†Head, Section of Epidemiology, and associate professor of preventive medicine, Sloan-Kettering Division of Cornell University Medical College.

‡Head, Research Design and Analysis Service, Sloan-Kettering Institute; head, Statistical Service Section, Cornell University Medical College.

§Member, Biometrics Branch, Division of Research Service, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

¶Assistant professor of preventive medicine, Sloan-Kettering Division of Cornell University Medical College; assistant director, Strang Cancer Prevention Clinic, Memorial Center for Cancer and Allied Diseases.

series show about 50 per cent of cases in women to be of the glandular type in contrast to 5 per cent to 20 per cent reported by different investigators among men. Epidermoid lung cancer and to a somewhat lesser extent undifferentiated lung cancer occur far more commonly among men.

Doll and Hill,[6] for example, found a male-female ratio among 43 cases of adenocarcinoma of 3.3:1.0 and ratios of 8:1 for 341 cases of the oat-cell and anaplastic types and 26:1 for 493 epidermoid lesions.

TABLE 1. *Death Rates from Lung Cancer in the United States.**

YEAR	RATE AMONG WHITE MALES	RATE AMONG WHITE FEMALES
	per 100,000	*per 100,000*
1930	3.6	2.1
1932	4.4	2.2
1934	5.3	2.8
1936	6.4	3.0
1938	7.8	3.1
1940	9.4	3.2
1942	10.4	3.5
1944	12.1	4.0
1946	14.4	4.0
1948	17.8	4.7
1950	19.5	4.3
1952	22.0	4.5
1954†	25.0	4.4

*Based on Vital Statistics.[1]
†Estimated.

Ochsner and his associates[7] observed a similar tendency among their cases. They reported a sex ratio of 1.7:1.0 for 71 cases of adenocarcinoma, 6.7:1.0 for 101 cases of undifferentiated and 19:1 for 164 cases of epidermoid cancer of the lung.

Wynder and Graham[8] noted a predominantly male ratio of 24:1 among 792 epidermoid and anaplastic cases whereas the ratio for 65 cases of adenocarcinoma was 2:1.

The same trend is demonstrated in a study conducted by the National Cancer Institute.[9] This 1947 study on morbidity from cancer in 10 American cities found a significantly larger percentage of adenocarcinoma of the lung for women than men. Among 1100 male patients 9 per cent were recorded as having had adenocarcinoma of the lung whereas of 191 female patients 27 per cent were reported to have this histologic type. On the basis of these figures Dorn and Cutler estimated a sex ratio of 2:1 for adenocarcinoma of the lung whereas this ratio was 13:1 for epidermoid lung cancer.

For this reason the present study was based on histologically proved cases.

METHOD OF STUDY

The present study is based on information about two different groups of women, 196 with histologically confirmed cases of cancer of the lung and 1304 who had cancer or benign tumors at sites other than the respiratory or upper alimentary tract. The latter group served as a comparison group. The 196 cases of lung cancer came from 11 different hospitals (Table 2). They include all available women with lung cancer admitted to the Memorial Center for Cancer and Allied Diseases during the period 1953

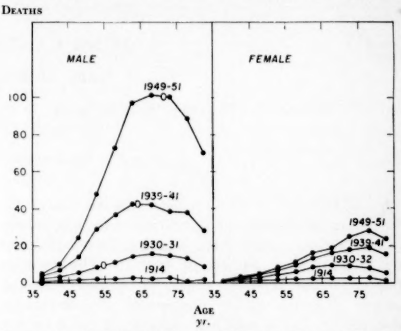

FIGURE 1. *Annual Deaths (per 100,000 Population) from Cancer of the Lung and Bronchus.*

to 1955. The histologic diagnosis was specially reviewed by Drs. John W. Berg and Fred W. Stewart.

In addition we obtained the co-operation of Drs. Richard H. Overholt, William L. Watson and Herbert C. Maier and their staffs, who kindly made the records of their patients available for this study. We have also had the assistance of the Delafield, St. Vincent's, Mount Sinai, Presbyterian, St. Luke's,

TABLE 2. *Distribution of Cases According to Hospital and Extent of Information Supplied.*

HOSPITAL	TOTAL CASES	PATIENTS INTERVIEWED	PATIENTS RETURNING QUESTIONNAIRES	PATIENTS NOT RETURNING QUESTIONNAIRES	PATIENTS NOT COMMUNICATED WITH IN ANY WAY
Memorial	67	40	12	7	8
Overholt Thoracic Clinic	38	0	19	19	0
Francis Delafield	16	2	6	8	0
Other*	75	5	21	26	23
Totals	196	47	58	60	31

*St. Luke's, Bellevue, Metropolitan, St. Vincent's, Mount Sinai, Lenox Hill & Presbyterian hospitals in New York & Peter Bent Brigham Hospital in Boston.

Bellevue and Metropolitan hospitals in the New York area. We are grateful to Drs. Morris A. Jacobs and Marta Fraenkel, who made it possible for us to obtain records of female patients with lung cancer in New York City hospitals. As in Memorial Center, only cases first diagnosed in 1953 to 1955 were included.

For each of the 196 cases in the study we obtained the age and histologic diagnosis. In 47 of the patients

it was possible to arrange for personal interview using the detailed questionnaire previously described to obtain information on smoking habits, previous employment and other environmental information of interest.[10] For the 149 noninterviewed patients a shorter version of this interview form was mailed to be completed either by close relatives or by friends who had known the patient for a long time, except in 31 patients for whom no address was available or with whom, for other reasons, we could not get in touch. Of the 118 questionnaires mailed 58 were returned (Table 2). The smoking habits and other environmental characteristics are based on the replies for the 105 patients who were interviewed personally or for whom completed questionnaires were received.

TABLE 3. *Distribution of Cases According to Hospital and Histologic Type.*

HOSPITAL	TOTAL CASES	EPIDERMOID CARCINOMAS	ADENOCARCINOMAS*	ANAPLASTIC CARCINOMAS†	UNCLASSIFIED CARCINOMAS	ADENOSQUAMOUS CARCINOMA
Memorial	67	30	26	3	8	
Overholt Thoracic Clinic	38	9	18	10		1
Presbyterian	18	3	9	6		
Lenox Hill	14	4	7	1	2	
Delafield	16	3	6	4	3	
Other	43	13	16	11	3	
Totals	196	62(32%)	82(42%)	35(18%)	16(8%)	1

*Including terminal bronchiolar.
†Undifferentiated.

These 105 patients are referred to as the "study group." The 1304 patients used for comparison purpose were all interviewed at Memorial Center during 1953 to 1955.

RESULTS

Histologic Evaluation

The distribution of the 196 cases by histologic type and hospital is shown in Table 3. On the basis of the broad classification used 32 per cent of the cases were epidermoid carcinoma, 42 per cent adenocarcinoma (including terminal bronchiolar), 18 per cent anaplastic or undifferentiated cancers and 8 per cent unclassified.

The variation between hospitals in the distribution of histologic type does not appear unusual, particularly in view of the small numbers involved. There does seem to be some tendency for Memorial Center to report a higher proportion of epidermoid cancer (45 per cent) than the others (25 per cent). Possible differences in interpretation by different pathologists must, of course, be kept in mind.

No matter what the precise figures are for the frequency of the different histologic types these data agree with those previously cited in showing that a sizable proportion of lung cancers among women are adenocarcinomas and that this proportion is considerably greater than that for males.

Age Distribution

The age distribution is shown in Table 4 for each of the histologic types and separately for women in the study group and others. It is interesting that the women with epidermoid cancer were somewhat younger than those with adenocarcinoma, the median age at onset being fifty-six for the epidermoid group and sixty-two for the adenocarcinomas (Fig. 2). The difference in median age at onset was much the same for women in the study group (105 patients for whom additional interview data were obtained) and for the others in the total group of 196 cases of lung cancer. The patients with anaplastic and undifferentiated carcinoma of the lung seemed to be intermediate in age, but the number of cases was too small to support any more detailed statement.

TABLE 4. *Distribution of Cases According to Age and Histologic Type.*

AGE	EPIDERMOID CARCINOMAS		ADENOCARCINOMAS		ANAPLASTIC CARCINOMAS		UNCLASSIFIED CARCINOMAS	
	STUDY GROUP	OTHER	STUDY GROUP	OTHER	STUDY GROUP	OTHER	STUDY GROUP	OTHER
yr.								
30 - 39	3	0	1	2	3	1	0	0
40 - 49	10	3	8	4	2	2	0	3
50 - 59	12	12	9	11	2	8	4	1
60 - 69	8	5	19	16	6	4	3	2
70	8	1	4	8	1	6	2	1
Totals	41	21	41	41	14	21	9	7

Occupation

No differences of any consequence in occupational distribution between the cases of lung cancer and comparison group or among the different histologic

types was apparent. The only known exposure to possible occupational respiratory irritants was noted among workers in clothing factories, who were exposed to lint. The majority of women studied were housewives and white-collar workers (Table 5).

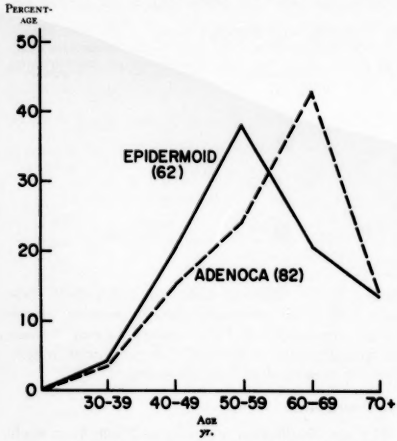

FIGURE 2. *Age Distribution of Female Patients with Cancer of the Lung According to Histologic Type.*

Previous Lung Complaints

Previous lung complaints were reported more frequently among the epidermoid carcinomas than among the adenocarcinomas. This difference was due in large part to the greater frequency of chronic cough in the former group (Table 5). The majority of the histories of chronic cough were given by patients who had been cigarette smokers.

Education

There were no significant differences in educational level among the three histologic groups or between them and the controls (Table 5).

Residence

There were no significant differences in place of residence, either before or after the age of twenty, among the three histologic groups. The comparison group contained more patients from large cities. This is a reflection of the fact that patients at Memorial Center with benign tumors are less likely to come from areas other than New York City.

Smoking

Data on female smoking are somewhat easier to evaluate than those of males because they include no pipe or cigar smokers. Table 6 records smoking habits separately for interviewed patients and for those for whom a mailed questionnaire was filled out. It will be seen that the differences between the two groups are small for each of the histologic types. These data are summarized in Table 7, which compares the distribution of the 47 interviewed patients with the distribution expected of 47 cases of the same histologic types, but with smoking habits as reported by questionnaire.

The difference between actual and expected is slight and not statistically significant. We have accordingly combined the 47 interviews and 58 questionnaires and treated them as one group in the subsequent analysis.

TABLE 5. *Distribution of Cases of Lung Cancer and Comparison Cases According to Certain Environmental Characteristics.*

ENVIRONMENTAL CHARACTERISTIC	DISTRIBUTION AMONG 41 EPIDERMOID CARCINOMAS	DISTRIBUTION AMONG 41 ADENOCARCINOMAS	DISTRIBUTION AMONG 23 ANAPLASTIC & UNCLASSIFIED CANCERS	DISTRIBUTION AMONG 1304 CONTROLS*
Occupation:				
Housewife	17	15	13	15
White-collar worker†	16	16	8	15
Factory worker‡	4	5	1	7
Domestic worker	4	3	1	2
Unknown	2	2	0	2
Previous lung disease:				
None	13	22	12	27
Bronchitis & chronic cough	11	6	4	6
Pneumonia	6	4	5	5
Pneumonia, bronchitis & chronic cough	9	6	0	2
Tuberculosis	0	1	0	1
Unknown	2	2	2	
Education:				
None	2	6	3	2
Grammar school	13	13	9	14
High school	16	15	5	16
Vocational school	2	2	0	3
College	8	3	3	6
Unknown	0	2	3	0
Residence:				
Before age 20:				
Rural	8	6	4	4
Town	4	6	5	5
Small city	8	4	2	3
Large city	17	19	10	27
Unknown	4	6	2	2
After age 20:				
Rural	3	1	0	1
Town	2	2	4	3
Small city	4	10	4	3
Large city	31	28	14	34
Unknown	1	0	1	1

*Expected distribution if 41 cases had characteristics of 1304 control cases.

†Includes saleswoman, secretary, office worker, teacher, nurse, manicurist, dressmaker & dancer.

‡Includes only workers in clothing industry (only known exposure to lint & materials).

Table 8 shows the distribution of the 1304 control cases by amount smoked, separately for each age group. Using the age distribution shown in Table 4 and these control results, we can compute the expected distribution in cases of lung cancer under the hypothesis that these patients and control patients of the same ages have the same smoking habits. This is a comparison of the smoking habits of these two groups, but with an adjustment for differences in age distribution. Such a comparison is shown in Table 9.

The most important finding is that there are more

smokers in the epidermoid group than one would expect on the basis of the control cases. Thus, 25 of the 41 patients with epidermoid cases, or almost 60 per cent, were smokers whereas the comparison group would lead one to expect no more than 11 smokers, or about 25 per cent. Furthermore, the smokers in the epidermoid group were heavier smokers than one would expect on the basis of controls. Thus, 12 of the 25 smokers with epidermoid carcinoma, or almost half, smoked more than a package of cigarettes a day, whereas on the basis of the control series only 1 in 11, or less than a tenth, would be expected to smoke so heavily. Much the same difference was shown for the anaplastic group, although the number of cases involved was smaller. No such differences appeared for the adenocarcinoma group, however: the observed number of smokers was only slightly above that expected, and, perhaps of even greater interest, the observed and expected numbers of smokers smoking one or more packages a day were equal.

TABLE 6. *Distribution According to Amount Smoked, Histologic Type and Source of Information.*

Average Daily Cigarette Consumption	Epidermoid Carcinomas		Adenocarcinomas		Anaplastic Carcinomas		Unclassified Carcinomas	
	Interview	Questionnaire	Interview	Questionnaire	Interview	Questionnaire	Interview	Questionnaire
0	7	9	12	17	1	4	7	2
1 - 9	2	1	0	4	1	1	0	0
10 - 19	4	6	3	4	1	2	0	0
20	7	5	1	0	1	3	0	0
Totals	20	21	16	25	4	10	7	2

TABLE 7. *Cigarette Consumption among Interviewed Patients and Those Reporting by Questionnaire.*

Average Daily Cigarette Consumption	Total Interviewed	Expected on Basis of Questionnaire Replies
0	27	28
1-9	3	4
10-20	8	9
21+	9	6
Totals	47	47

Epidermoid lung cancer develops at a significantly earlier age in smokers than in nonsmokers. In this group there were 20 cases before the age of sixty among the smokers and only 5 after that age. For the nonsmokers this situation was reversed. Thus, only 5 cases of epidermoid lung cancer developed among nonsmokers before the age of sixty, but 11 after. On the other hand, in the adenocarcinoma group, in which there were 12 smokers, cancer developed in 7 before and in 5 after the age of sixty. Among the 29 nonsmokers with adenocarcinoma there were 11 cases before and 18 after the age of sixty. The median age of female patients with epidermoid lung cancer who were smokers is fifty-two and a half as compared to sixty-six and a half for the nonsmokers, a difference of fourteen years. The median age of the 11 smokers with adenocarcinoma was fifty-eight and a half as compared with sixty-two and a half for the 30 nonsmokers.

There are enough cases involved to establish that smokers have an earlier age at onset of epidermoid lung cancer than nonsmokers. The question of whether this difference is larger for the epidermoid than for the adenocarcinoma cases must remain open, however. Furthermore, since among the control patients the smokers have an earlier age at onset of the "control ailment" than nonsmokers do, these results may merely reflect the fact that in any cross-section female smokers tend to be a younger group than nonsmokers.

Table 10 shows the distribution of 25 epidermoid lung cancers according to the duration of smoking. Comparison with the distribution to be expected on the basis of the duration of smoking for control patients of the same age discloses no characteristic differences.

TABLE 8. *Distribution of Control Patients According to Age and Amount Smoked.*

Age	No. of Patients	Patients Smoking 0 Cigarettes Daily	Patients Smoking 1 - 9 Cigarettes Daily	Patients Smoking 10 - 20 Cigarettes Daily	Patients Smoking 21 + Cigarettes Daily
yr.		%	%	%	%
30 - 39	225	51	17	26	6
40 - 49	429	55	13	28	5
50 - 59	354	72	8	18	2
60 - 69	219	85	6	7	1
70+	77	90	7	4	0

Male-Female Comparison Smoking Study

To ascertain the smoking habits of men and women, 205 white males and 205 white females were matched for age, education and diagnosis (benign conditions or cancers of systems other than the respiratory), and the smoking histories compared. Men who smoked pipes and cigars were excluded to allow for a better comparison between males and females. The following results were obtained:

Age by Percentage of Nonsmokers

The percentage of nonsmokers is significantly higher for the females than the males for all the age groups. For the females, the percentage of nonsmokers in the age group from sixty to sixty-nine is significantly higher than that in the group from thirty to thirty-nine and the trend is apparent throughout (Fig. 3).

TABLE 9. *Distribution According to Amount Smoked and Histologic Type (Comparison of Observed and Expected Number).*

SMOKING STATUS	EPIDERMOID CARCINOMAS		ADENOCARCINOMAS		ANAPLASTIC CARCINOMAS		UNCLASSIFIED CARCINOMAS	
	OBSERVED	EXPECTED*	OBSERVED	EXPECTED*	OBSERVED	EXPECTED*	OBSERVED	EXPECTED*
Nonsmoker	16	30	29	32	5	10	9	7
Smoker:	25	11	12	9	9	4	0	2
1 - 9/day	3	4	4	3	2	2	0	1
10 - 20/day	10	6	7	5	3	2	0	1
21/day	12	1	1	1	4	0	0	0

*On basis of smoking habits of controls of comparable ages.

For the males the percentage of nonsmokers remains fairly constant over all the age groups — that is, there is no significant difference among any of the age groups.

Age by Average Duration

The average duration of cigarette smoking is consistently higher for the males than for the females, though in the age groups from thirty to thirty-nine and forty to forty-nine the difference is not statistically significant whereas in the groups from fifty to fifty-nine and sixty to sixty-nine the difference is statistically significant. It is in the last two age groups that cancer of the lung is most frequent (Fig. 4).

The important point to note is the fact that for the males the curve for age by average duration is roughly linear — that is, the men from sixty to sixty-nine years of age have smoked for about ten years longer than those from fifty to fifty-nine. However, for females the average duration levels off, and the women between sixty and sixty-nine have smoked about as long as those between forty and forty-nine years of age. In other words the older women started smoking later in life and have not smoked as long as the men have.

Age by Percentage Smoking More than Twenty Cigarettes a Day

The percentage of smokers of more than a package a day is significantly higher for the males than for the females in the groups over forty years old. In the group from thirty to thirty-nine the difference is not statistically significant (Fig. 5).

For both the males and females the percentage smoking more than a package a day is lowest in the group from sixty to sixty-nine years of age, but the difference is not significant. However, in females, there are too few cases to establish any significance.

DISCUSSION

The infrequency of cancer of the lung in women leads to a small series in relation to the reported male series. To utilize to the fullest extent the cases that were available it was necessary to adopt several expedients not used in the study of males. Thus, we used information on age and histologic type for 31 patients from whom we were unable to obtain additional information. In 118 cases we resorted to mailed questionnaires. Only half these were returned, and for the half returned, the respondent was often not the patient. It is noteworthy, despite the possible sources of error in data collected in this fashion, the smoking histories yielded by the interview and by the questionnaires returned agreed quite closely. Although the accuracy of smoking histories obtained even in carefully controlled interviews is sometimes questioned, this agreement suggests to us that there is something to be said for the general, common-sense point of view that nonsmokers and heavy smokers can easily be distinguished from each other, and that the reporting of smoking history is unlikely to be a serious source of error in studies of this type.

TABLE 10. *Relation of Duration of Smoking to Occurrence of Epidermoid Cases and Expectation on the Basis of Controls of Similar Ages.*

DURATION OF SMOKING	ACTUAL NO. OF EPIDERMOID CASES	EXPECTED NO. OF EPIDERMOID CASES
yr.		
1-9	2	2
10-19	6	6
20-29	7	9
30-39	8	5
40+	1	2
Unknown	1	1
Totals	25	25

Histologic Types

The results of this study agree with those of Wynder and Graham[8] in showing that adenocarcinomas occur with little if any greater frequency among smokers than among nonsmokers. This contrasts with the marked relation for epidermoid cancers of the lung. The anaplastic or undifferentiated lung-cancer group appears to behave more like the epidermoid group in

this respect. A small group of cases are listed as carcinoma of the lung unclassified. We have too few cases to make definitive remarks, but it is of interest that none of these patients have smoked. It is sometimes suggested that the excess of smokers in the lung-cancer group consistently found in studies of this type among males may be spurious, and could arise because the preconceptions of the attending physician lead him to diagnose doubtful cases as lung cancer if the patient smokes and something else if he does not. The present results can be explained on this basis only if one imputes to the pathologist an additional preconception that leads him to diagnose doubtful cases as epidermoid if the patient smokes and adenocarcinoma or something else if he does not.

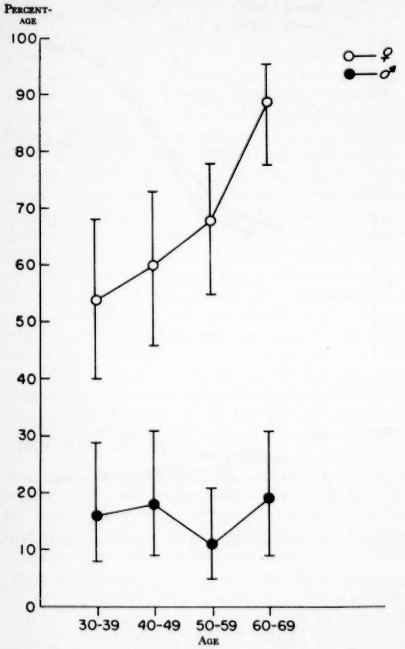

FIGURE 3. *Percentage of Nonsmokers by Age and Sex. The solid circles indicate male, and the open circles female patients. The vertical lines are 95 per cent confidence limits.*

To check on the possibility we have had the slides on the 41 lung-cancer cases seen at Memorial Hospital reviewed by Drs. John W. Berg and Fred W. Stewart. This review was done without knowledge of the histologic type previously found or of smoking history. In 4 of the 41 cases the diagnosis was changed. All 4 had previously been diagnosed as epidermoid and on review were rediagnosed as adenocarcinomas. One was a nonsmoker, 1 smoked less than half a package a day, and 2 smoked a package or more per day. This review results in no essential change in our findings, and makes it difficult to argue that these results are spurious because of the use of smoking history as an aid in diagnosis.

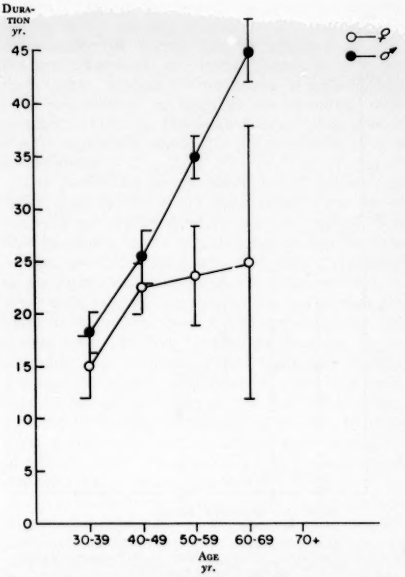

FIGURE 4. *Duration of Cigarette Smoking by Age and Sex. The solid circles indicate male, and the open circles female patients. The vertical lines are 95 per cent confidence limits.*

Female Controls

The data on the smoking habits of control women were obtained by personal interview. Such results are useful only to the extent that they faithfully portray the smoking habits of all women in the population from which the lung-cancer cases arose. Figure 6 compares the reported smoking habits of the controls in the present study with those obtained by the United States Bureau of the Census in a sample survey of the general population made at the request of the National Cancer Institute.[11] It will be observed that the two sets of results are in substantial agreement. Both show that about half the female population of thirty years of age consists of nonsmokers, and that this fraction increases with age until at the highest age group 90 per cent of the women are nonsmokers. They both show also that smokers of more than a package a day are infrequent at all age groups. This level of smoking is reported by only 4 or 5 per cent

of the female population even at the age of thirty, and by the age of sixty not more than 1 per cent smoke this much.

In summary the accuracy of the smoking histories and the pathological diagnosis have stood up under whatever critical examination it has been possible to subject them to.

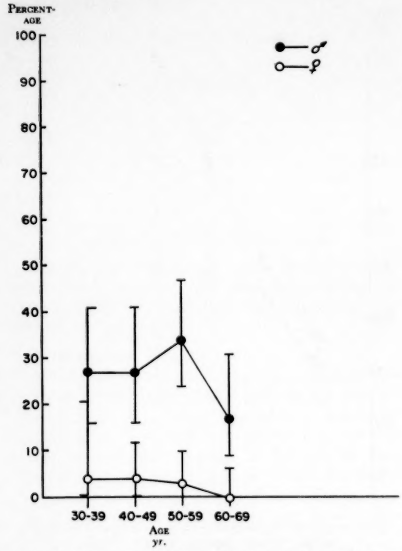

FIGURE 5. *Percentage Smoking More than Twenty Cigarettes a Day by Age and Sex.*
The solid circles indicate male, and the open circles female patients. The vertical lines are 95 per cent confidence limits.

Statistically significant variables in an epidemiologic survey having been established, it remains to be determined how these variables can account for the general incidence pattern of a particular cancer. If a given variable can account, at least in part, for these observations, the variable gains significance. It will be of particular interest to determine how the three most commonly suspected factors in the development of lung cancer — smoking, residence and occupation — can account for the development of lung cancer in women, on the basis of data here presented, as well as on the basis of the general incidence pattern of lung cancer.

Sex Ratio

The changing ratio of male to female lung-cancer cases has been one of the most intriguing clues in the problem. This changing sex ratio provided major support for the belief that the majority of increase in lung cancer observed today is real, since improved diagnostic means in a population group would affect the female as well as the male rates. Consequently, a reasonable working hypothesis would be that there was a factor to which men were exposed more than women. Both smoking and occupational exposures could fit this category, except that studies on occupational exposures among lung cancer in men have shown that though there are a few occupational exposures that seem to carry an increased risk, the majority of cases in men cannot be accounted for by the occupational exposures.[10,12-14] The factor of air pollution is also not likely to account for much of this difference in sex ratio since, in general, as far as is now known, women are as much exposed as men

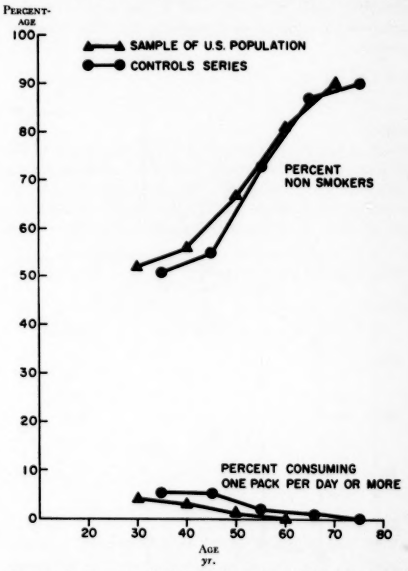

FIGURE 6. *Smoking Habits in Women — National Sample and Control Series by Age.*

to whatever polluted air there may be in city areas unless this is linked to industrial exposure. It is sometimes argued that if cigarette smoking were a major factor in the etiology of lung cancer, women should have the same rate as men, since they smoke as much. The control data indicate clearly that women still smoke less than men, at least at all ages above thirty, and that in the cancer age groups the smoking female is still the exception, and the heavily smoking female a rarity. These results are obviously consistent with the fact that lung cancer is more frequent among males than among females. Recent calculations by Haenszel et al.[12] indicate that the male-female differences in smoking habits could be expected to lead to an incidence among males approximately four times that of females — that is, to the observed sex ratio.

In such a calculation it is necessary to assume as a working hypothesis the equal incidence of lung cancer for men and women with the same smoking histories. That this hypothesis leads to a correct estimate of the sex ratio for lung cancer is indirect evidence in its favor. We may use the results of the present study to investigate this hypothesis in a more direct fashion. At first sight one might be inclined to conclude that the present results are inconsistent with the hypothesis that equal exposure to tobacco results in equal incidence of lung cancer for both sexes. Sixteen of the 41 patients with epidermoid cancer, or 40 per cent, were nonsmokers, whereas among cases of lung cancer among men, the percentage of nonsmokers is a good deal smaller, varying from 1 to 5 per cent. If heavy smokers have a high incidence, regardless of sex, how, one might ask, can 40 per cent of the female patients with lung cancer be nonsmokers?

To understand how this can occur it is best to consider an arithmetic example. One might imagine a population of 10,000,000 adults, half male and half female, in which, in any one year, lung cancer develops in 5 out of every 100,000 nonsmokers, whether male or female. Similarly, it is to be supposed that of the smokers, whether male or female, lung cancer develops in 30 out of every 100,000. In such a hypothetical community tobacco is a fundamental factor in the development of lung cancer, whereas sex is not a factor at all. Finally, it is to be supposed that of the males only 20 per cent are nonsmokers, and of the females 80 per cent are. The expected pattern of lung cancer among smoking and nonsmoking males and females in this community is then analyzed. Of the 5,000,000 males 1,000,000, or 20 per cent, are nonsmokers, and lung cancer develops in 5 out of every 100,000 of them, or 50. Of the 4,000,000 male smokers lung cancer develops in 30 out of every 100,000, or 1200. Of the 1250 male patients with lung cancer 50, or 4 per cent, are nonsmokers. Of the 5,000,000 females the only difference is that 80 per cent are assumed to be nonsmokers. Lung cancer develops in 5 out of every 100,000 of them, or 200, whereas among the 1,000,000 smoking females, lung cancer develops in 30 out of every 100,000, or 300. Of the 500 female patients with lung cancer 40 per cent are nonsmokers. In short, in this hypothetical community in which the risk of lung cancer depends on amount smoked and not on sex, the lower frequency of smoking among females results in both a relatively higher incidence of lung cancer among men and a higher percentage of nonsmokers among female patients with lung cancer.

To study the possible effects of sex on the development of lung cancer it is thus not correct to investigate the frequency of smokers among the patients with lung cancer in the two sexes since this could vary even when the effect of tobacco on the development of lung cancer is the same for both sexes. One must instead investigate the incidence of the disease among smoking and nonsmoking males and females.

Unfortunately, the female series is not large enough to allow more than a very rough estimate. According to Cornfield's[15] method the risk for a female smoker (compared with that for a female nonsmoker) is 4.3 (with 95 per cent confidence limits of 2.0 to 8.1). A corresponding relative risk estimate for males is 7.5 (based on a combination of 14 studies of lung cancer in men).[16] Hence, the data do not permit any definite answer to the question whether or not there are sex differences. The relative risk for females is smaller, but not significantly so. It has already been shown that women smokers do not smoke as heavily, and have not smoked as long, as corresponding male smokers. Therefore, the smaller female risk, even if it were significant, would still not necessarily show a sex difference.

The possibilities for the prediction of future lung-cancer rates in women are also limited by the size of the series and the need for various assumptions. The fact that even in the youngest age groups half the women are nonsmokers and that only 5 per cent smoke as much as a package a day suggests that although the rate will continue to increase through the years, it is unlikely that it will approach the rate among males. In fact, calculations based on the assumption that twenty-five years from now a sixty-five-year-old woman will smoke as much as a forty-year-old woman now does suggest that the lung-cancer rate for women is unlikely to increase by more than twofold in the next twenty-five years on account of tobacco alone. The distribution of histologic types discussed above accounts in part for the gradual increase in mortality from lung cancer in women that is predicted here. It was shown that over half the cases are histologic types in which smoking appears to have little influence. Hence, any increase in epidermoid lung cancer is "diluted" by the other histologic types. Thus, if the incidence from epidermoid lung cancer were to increase by 50 per cent the over-all lung-cancer rate would increase by only 25 per cent.

Age Distribution

The curve relating the incidence of lung cancer to age differs from that for other major cancers, in that it has a marked upswing until the late fifties but does not continue to rise with increasing age. It has been suggested that this peculiar drop in the incidence of lung cancer was consistent with the fact that the younger group of males had taken up the cigarette to a greater extent than men of the older age groups. It has been pointed out that air pollution could not account for such an age curve because once the air becomes polluted by a given factor all age groups are exposed to this factor at the same time.

If, as the present study indicates, the incidence of epidermoid, but not adenocarcinoma of the lung is related to smoking, one should expect, in line with the results in males, the age-incidence curve for the epidermoid type but not the adenocarcinoma to show the same peculiar drops. Kreyberg[17] has analyzed the

Norwegian experience to obtain age-incidence curves separately for the different histologic types. They show what one would expect on this hypothesis: that the types unrelated to tobacco use show an increasing incidence with advancing age, whereas the types related to tobacco use rise to a peak and then drop.

Miscellaneous Factors

Review of occupational histories revealed no significant differences between the different histologic types of lung cancer, nor were we able to determine significant differences for residence. The only other factor of interest that was noted was the greater prevalence of chronic cough and bronchitis among patients with epidermoid cancer of the lung than for those with glandular cancer of the lung and for controls. The data, however, suggest that this relation may be attributable to the greater cigarette consumption among the former group.

Evaluation

Basis of Demonstration

The principles of a scientific demonstration have been so widely misunderstood and disregarded in the current controversy over smoking and lung cancer that we wish to present a formal outline of the logical steps employed here to go from the basic data to conclusions.

The first step is to list alternative hypotheses that have been proposed. These hypotheses, being too numerous to list in detail, are divided into four broad categories:

I. The results are due to sampling variation alone (that is, the kind of differences that will occur even when two samples are drawn from the same population).

II. The results are due to artifacts or biases (that is, the measuring instrument — here a questionnaire — or the method of obtaining the sample or to other procedures used in the collection and processing of the data).

III. The results are due to "accepted" factors (that is, in epidemiologic studies, such factors as age and sex for which extensive evidence of relations already exists).

IV. The results are due to "proposed" factors (that is, factors that have been suggested in the literature but for which extensive evidence is lacking).

The logical principle of scientific demonstration is to supply a process of elimination to the list of hypotheses, eliminating hypotheses that, in view of the basic data, are highly unlikely. The principle of scientific simplicity (Occam's razor) requires that we proceed down this list of categories of hypotheses. In other words we shall not propose a new hypothesis if a simpler explanation is available.

The application of this procedure to the data summarized in the preceding section is outlined as follows:

I. The statistical methods (significance tests) used here indicate that it is extremely unlikely that the differences between the smoking habits of the women in the series of cases of epidermoid lung cancer and those of the women in the comparison series are due to sampling variation alone. On the other hand it is not unlikely that the differences between the adenocarcinoma series and the control series and between the control series and the national sample are due to sampling variation alone.

II. A statistical examination of the basic data suggests that it is unlikely that there are sizable biases or artifacts (slight biases could not account for the markedly different smoking habits found in the epidermoid series):

a. It is unlikely that there are sizable biases in the measuring instrument because two different instruments (an interview and a mailed questionnaire) were used, but the results were very similar in both cases.

b. It is unlikely that there were sizable biases in the histologic classifications because an independent review by expert pathologists gave similar classifications.

c. It is unlikely that there were sizable biases in the selection of the epidermoid series because such a bias should also have appeared in the adenocarcinoma series. The adenocarcinoma series provides an especially good control series because the two types of cancer can be distinguished only by a microscopical examination of lung tissue. This is a unique feature of this study.

d. It is unlikely that there were sizable biases in the selection of the comparison series. The similarity of the adenocarcinoma series, the control series and the national sample affords a striking validation of the sample — a degree of validation that is rarely possible in epidemiologic studies.

III. Statistical analysis of the data reveals that it is highly unlikely that the results are due to age. Sex is not a variable since all the subjects in the primary series are women. As a precaution several different analyses have been run adjusting for age only, age and education and so forth. All these different analyses lead to the same conclusion.

IV. A strong effort was made to include in the interviews all the factors that have been suggested as bearing on the etiology of lung cancer, such as occupational exposure, air pollution (residence) and previous medical history. No demonstrable difference was found between the series for these factors. This does not mean that these factors play no part, because with relatively short series it is only possible to detect very strong environmental factors.

However, it does mean that it is highly unlikely that the results are due to these factors alone or to correlations between these factors and smoking.

As a result of this process of elimination we are left with the hypothesis that cigarette smoking substantially increases the risk of epidermoid lung cancer in women. In accordance with scientific principles we are entitled to assert this hypothesis as a "posit" (as the most probable hypothesis on the basis of our evidence). This is all that can be demonstrated in any field of science, including the physical sciences. We note that we are unable to reject the hypothesis that cigarette smoking does not increase the risk of adenocarcinoma of the lung in women.

In addition to the data of this study there is the evidence from vital statistics as well as previous data on lung cancer; therefore, the posit can be tested against the other data. This has been done and it has been found that the posit is consistent with the following:

The United States Vital Statistics on the death rate from lung cancer in males and females over the past decades. In particular both the lower death rate among females and the slower rise in this death rate can be explained by this posit. According to our posit the rate should not rise very much in the next decade (a twofold increase is unlikely even though the younger women are smoking more heavily than the older women).

The change in the sex ratio in lung cancer in the preceding decades.

The relative frequency of adenocarcinoma and epidermoid lung cancer in males and females, as well as the changes in this relative frequency over the past decades in the two groups.

Previous studies of the relation between smoking and lung cancer in males.

The posit not only is consistent with the body of data known to us but also resolves some of the apparent paradoxes concerning lung-cancer rates in women. We therefore assert the posit that cigarette smoking increases the risk of epidermoid lung cancer in women.

Summary

The primary focus of this study was on the smoking habits of women in three groups: women with epidermoid lung cancer; women with adenocarcinoma of the lung; and women with tumors at certain other sites (controls). It was found that the smoking habits in the last two groups were similar. The smoking habits in the last group were similar to those in a large sample of women in the general population of the United States. The smoking habits in the first group were markedly different from those in the last two in that a much larger proportion of women in the first group smoked cigarettes and the smokers in that group smoked more heavily (that is, the proportion of those smoking a package or more a day was higher).

In the control group, as in the sample of the United States female population, the smoking habits of the women change with age: about half the women under fifty and most of the women over fifty are nonsmokers; and less than 2 per cent of the women over fifty smoke as much as a package a day (the proportion is more than twice as great in the women under fifty).

The smoking habits of the women in the control group are minimal compared to the smoking habits in a control group of male patients: the vast majority of men over forty use tobacco, and a large majority of the women in this age group do not use tobacco; a majority of the men over forty who smoke cigarettes will consume at least a package a day whereas only a small minority of the women over forty who smoke cigarettes consume this much; and, finally, even in the age groups under forty, the women with tumors at other sites (control group) have minimal smoking habits in relation to the male controls.

We are indebted to Mrs. Sarah Moffett and Mrs. Rivkah Feldman for assistance in the compiling and statistical analysis of the data.

References

1. Vital Statistics of the United States and the United States Bureau of the Census Current Population Reports. Population estimates. Series P-25.
2. Doll, R. Etiology of lung cancer. In *Advances in Cancer Research* (1955). Vol. 3. Edited by J. P. Greenstein and A. Haddow. 369 pp. New York: Academic Press, 1955. Pp. 1-50.
3. Adler, I. *Primary Malignant Growths of the Lungs and Bronchi: A pathological and clinical study.* 325 pp. New York: Longmans, Green & Co., 1912.
4. Walshe, W. H. *The Anatomy, Physiology, Pathology and Treatment of Cancer.* 351 pp. Boston: William D. Ticknor & Co., 1844.
5. Doll, R. Bronchial carcinoma: incidence and aetiology. *Brit. M.J.* **2**:521-527 and 583-590. 1953.
6. Doll, R., and Hill, A. B. Study of aetiology of carcinoma of lung. *Brit. M. J.* **2**:1271-1286, 1952.
7. Ochsner, A., DeCamp, P. T., DeBakey, M. E., and Ray, C. J. Bronchiogenic carcinoma: its frequency, diagnosis, and early treatment. *J.A.M.A.* **148**:691-697, 1952.
8. Wynder, E. L., and Graham, E. A. Tobacco smoking as possible etiologic factor in bronchiogenic carcinoma: study of six hundred and eighty-four proved cases. *J.A.M.A.* **143**:329-336, 1950.
9. United States Public Health Service. *Cancer Morbidity Series, 1950-1952.* (Reports 1-10.) (Report 1.) Cutler, S. J. *Cancer Illness: Among residents of Atlanta, Georgia, 1947.* 45 pp. *(United States Department of Health, Education and Welfare, Public Health Service Publication* No. 13.) Washington, D.C.: Government Printing Office, 1950.
10. *Idem. Cancer Morbidity Series, 1950-1952.* (Reports 1-10.) (Report 2.) Grodowitz, W. *Cancer Illness: Among residents of San Francisco and Alameda Counties, California, 1947.* 46 pp. *(United States Department of Health, Education and Welfare, Public Health Service Publication* No. 65.) Washington, D.C.: Government Printing Office, 1951.
11. Wynder, E. L., Bross, I. J., and Day, E. Epidemiology approach to etiology of cancer of larynx. *J.A.M.A.* **160**:1384-1391, 1956.
12. Haenszel, W., Shimkin, M. B., and Miller, H. Tobacco smoking patterns in United States. In *Public Health Monograph* No. 45. 963 pp. Washington, D. C.: United States Department of Health Education and Welfare, 1956.
13. Wynder, E. L., and Graham, E. A. Etiologic factors in bronchiogenic carcinoma with special reference to industrial exposures: report of eight hundred fifty-seven proved cases. *Arch. Indust. Hyg.* **4**:221-235, 1951.
14. Breslow, L. Industrial aspects of bronchiogenic neoplasms. *Dis. of Chest* **28**:421-430, 1955.
15. Cornfield, J. Method of estimating comparative rates from clinical data: applications to cancer of lung, breast and cervix. *J. Nat. Cancer Inst.* **2**:1269-1275, 1951.
16. *Idem.* Statistical problem arising from retrospective studies. In *Berkeley Symposium on Mathematical Statistics and Probability: Proceedings of the third symposium held at the Statistical Laboratory, University of California, December 1954, July and August, 1955.* 5 vol. Edited by J. Neyman. Berkeley: University of California Press, 1956. Vol. 4.
17. Kreyberg, L. Geographical distribution of histological sub-groups of primary epithelial lung tumors in Norway. *Brit. J. Cancer* **8**: 599-604, 1954.

INTRACAVITARY ADMINISTRATION OF RADIOACTIVE COLLOIDAL GOLD (Au^{198}) FOR THE TREATMENT OF MALIGNANT EFFUSIONS*

A Report of Thirty-one Cases and an Appraisal of Results

MELVIN P. OSBORNE, M.D.,† AND BRADLEY E. COPELAND, M.D.‡

BOSTON

THE therapeutic use of radioactive colloidal gold (Au^{198}) was first described by Sheppard et al.,[1] who reported on intravenous use in 1947. Its possibilities for the treatment of various malignant processes have been explored in great variation. It is the purpose of this paper to appraise the results in the treatment of malignant peritoneal and pleural effusions in 31 patients seen at the New England Deaconess Hospital since August, 1951. The series is consecutive, and all patients have been traced.

This material is produced by irradiation of gold foil in an atomic nuclear reactor pile, solution of the activated foil in aqua regia, neutralization and reduction by ascorbic acid (in the presence of gelatin) to metallic gold particles. Radiation emitted consists of a strong beta particle (0.98 Mev), which has a maximum penetration range through tissues of 3.8 mm., a "half path" of approximately 0.4 mm. and half life of two and seven-tenths days. Only three days in the hospital are required after injection of 100 millicuries of Au^{198} so far as radiation hazards are concerned.

The effective but essentially nonpenetrating beta radiation released from the active gold particles determines the sharp localization of radiation effects produced. Thus, ionizing radiation occurs only in tissues in very close proximity to the gold particles. The gold is chemically inactive. When introduced intravenously, it localizes in the reticuloendothelial system throughout the body,[2-4] and activity is demonstrated in greatest concentration over the spleen and liver and, to a very slight degree, in the bone marrow. Direct injection into tumor masses[5] is associated with effects confined to the tissues of the mass injected. Zeidman, Copeland and Warren[6] reported absence of lymphatic systems in tumors themselves, and this seems to limit the amount of radiation that can be delivered to metastatic tissue via the lymphatic system. Interstitial injection[7] is followed by rapid phagocytosis of gold particles, taking up of the material into lymphatic drainage systems and localization in the regional lymph nodes draining the area injected. Many studies have shown that localization in the lymph nodes delivers effective radiation there, but that when metastatic tumor is present in the nodes, gold is found in the normal, functioning portion of the node rather than the tumor-containing areas.[8] The gold has been placed in the urinary bladder for superficial radiation.[9] It has been employed for "prophylactic" thoracic-cavity treatment after resection of pulmonary neoplasms[10] and has been injected directly into bronchi[11] and into the pulmonary artery.[12]

When the colloidal suspension of gold particles is introduced into a fluid-containing serous cavity, there

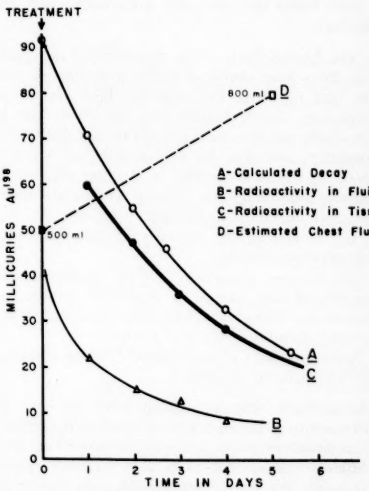

FIGURE 1. *A Graphic Representation of the Distribution of Radiation after Treatment of a Pleural Effusion. Measured amounts of radioactivity were observed in samples of fluid withdrawn daily. The residual fluid after initial aspiration and treatment and its increase were estimated from x-ray study* (D). *As this volume increased, radiation present in the fluid was calculated* (B); *only this amount is ineffective. The decay of the initial dose used is represented* (A). *Subtraction of values along curve* B *from those of curve* A *reveals curve* C, *which depicts radioactivity actually present at the pleural surfaces.*

is an initial rapid, wide diffusion of the material throughout the fluid and then quick disappearance of the gold as it becomes localized on the surface of the serous cavity. Figure 1 shows the disappearance of radioactivity from fluid samples withdrawn serially from the chest of a patient (Case 8, Table 1).

*From the New England Deaconess Hospital and the Cancer Research Institute.

This program was made possible by Atomic Energy Commission Contract AT(30-1)-901.

†Clinical associate in surgery, Harvard Medical School; surgeon, New England Deaconess Hospital.

‡Instructor in pathology, Harvard Medical School, clinical pathologist, New England Deaconess Hospital.

TABLE 1. *Results of Au^{198} Treatment of Pleural Effusion Due to Malignant Tumors.*

Case No.	Patient	Sex	Age	Pathological Diagnosis	Medical History	Treatment	Survival	Result
			yr.				mo.	
Determinate Group 1 (benefit)*:								
1	J.H.	M	76	*Lung carcinoma* (cytology of fluid)	Large lung tumor, with mediastinal mass, pleural spread & fluid; x-ray treatment; thoracenteses every 2 wk.	Left pleura, 102 mc.	5	Chest dry up to time of death
2	M.K.	F	49	*Breast carcinoma* (specimen & cytology of fluid)	Mastectomy 3 yr. before & then radium sterilization; pleural effusion known for 1 yr.; 8 thoracenteses done.	Left pleura, 69 mc.; patient expectorated gold & showed radioactivity over right hemithorax.	12	Chest remained dry until death from effects of disease elsewhere
3	E.J.	F	63	*Ovarian carcinoma* (specimen & cell block on fluid)	Hysterectomy & oöphorectomy for ovarian carcinoma 8 mo. before; pleural recurrence with fluid; 8 thoracenteses before Au^{198} instillation.	Right pleura, 96 mc.	27†	1 thoracentesis early after treatment; good result; asymptomatic; chest dry; patient living.
4	A.P.	F	71	*Breast carcinoma* (specimen & cytology of fluid)	Mastectomy 3 yr. before; 2 pretreatment taps, with rapid reaccumulation; patient died of pulmonary embolism just before planned treatment of 2d side.	Left pleura, 94 mc.	5	Chest dry at death; only microscopic tumor in pleural scar at autopsy.
5	A.T.	F	73	*Breast carcinoma* (specimen & cytology of fluid)	Mastectomy 3 yr. before; 4 thoracenteses, weekly, before treatment.	Right pleura, 103 mc.	4	Chest remained dry; death from extensive liver & mediastinal tumor spread.
6	T.K.	F	63	*Breast carcinoma* (specimen & cytology of fluid)	Mastectomy 5 yr. before; parenchymal & pleural tumor spread; 3 thoracenteses in mo. before treatment.	Left pleura, 92 mc.	7	3 post-treatment thoracenteses; then chest dry for 5 mo. to death.
7	M.G.	F	44	*Ovarian carcinoma* (specimen & cytology of fluid)	Hysterectomy & oöphorectomy for extensive tumor 2 mo. before; bilateral effusions & ascites developed; super-voltage x-ray treatment & "many" thoracenteses; bowel perforation by abdominal trochar.	Right pleura, 104 mc.; left pleura, 102 mc.	2	Fluid present on x-ray study; no thoracentesis needed up to death.
8	H.D.	F	65	*Breast carcinoma* (specimen & cytology of fluid)	Mastectomy 7 yr. before; control of chest-wall & pleural recurrence with stilbestrol & x-ray therapy until previous 3 mo.; 6 thoracenteses before treatment.	Left pleura, 100 mc.	5†	Two post-treatment taps; chest now dry for 3 mo.
Determinate Group 2 (no benefit)‡:								
9	F.S.	F	41	*Breast carcinoma* (specimen & cell block of pleural fluid negative before radiation given)	Mastectomy 2 yr. before; x-ray sterilization; super-voltage x-ray therapy; hormones (male) given; 2 thoracenteses before gold instillation.	Left pleura, 75 mc.	3	Post-treatment thoracenteses required; no benefit seen.
10	H.A.	F	51	*Breast carcinoma* (specimen & cytology & cell block positive on fluid)	Mastectomy 9 yr. before; pleural fluid accumulated for 2 yr.; "many" thoracenteses; irradiation & hormones (male) given for pleural & bone metastasis.	Right pleura, 105 mc.	2	No benefit seen; fluid reaccumulated rapidly up to time of death.
Indeterminate Group 3§:								
11	J.M.	M	30	*Hodgkin's disease* of lung (biopsy)	11 yr. of illness, with mediastinal, pleural & pulmonary tumor; many thoracenteses.	Left pleura 86 mc.	3/4	Patient moribund when treated & died too soon for pleural response
12	C.M.	M	63	*Peritoneal & pleural carcinoma* ?origin (biopsy)	Patient ill for 3 mo.; bilateral pleural & peritoneal effusions; biopsy at laparotomy; no site of origin identified.	Right pleura, 98 mc.; peritoneum treated 11 days later.	2/4	Very rapid deterioration in moribund patient; survival too short to evaluate response.
13	E.W.	F	47	*Ovarian carcinoma* (specimen & cytology of fluid)	Patient had pelvic exenteration for ovarian carcinoma 5 mo. before treatment	Left pleura, 100 mc.; right pleura, 124 mc. 8 days later.	3/4	Early death; no benefit possible.
14	M.P.	F	47	*Breast carcinoma* (specimen & cytology of fluid)	Mastectomy 2 yr. before; x-ray treatment, without benefit, for pleural & bilateral parenchymal lung spread; taps every 3 days required.	Right pleura, 106 mc.	1/4	Early, sudden death; no benefit possible.

*Pleural-fluid accumulation effectively stopped by treatment.
†Patient living.
‡Early death; no benefit from Au^{198}.
§Disease far advanced; death too early for evaluation of Au^{198} effect.

The gold particles remain in phagocytes and occasionally in lymphatics of the tissues of the serous surfaces, and almost all radiation is delivered into these surface tissues.* An avascular fibrosis results, and metallic gold particles along with tumor cells are entrapped in the pleura. In 1 case (Case 4, Table 1), there had been effective control of a malignant pleural effusion for five months; at autopsy, despite extensive parenchymal lung metastasis, no fluid was present in the treated chest, whose pleura was entirely fused with the fibrous reaction shown in Figure 2.

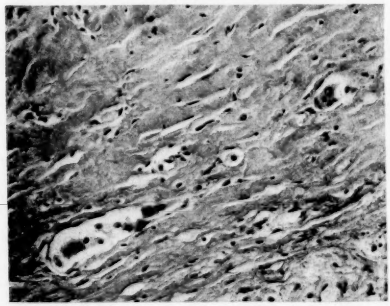

FIGURE 2. *Section from the Subpleural Lung (Case 4, Table 1), Showing a Tumor Cell Entrapped in Dense, Hyalinized Scar Five Months after Au^{198} Treatment.*

The methods for intracavitary administration of this radioactive material developed and used at New England Deaconess Hospital have been reported by Rose, Osborne and Stevens.[13] Delivery into the chest is made by thoracentesis needle, and abdominal administration is accomplished through a trochar or with catheters introduced at operation.

PERITONEAL EFFUSIONS

We have treated peritoneal effusions due to disseminated cancer with doses between 87 and 107 mc. of radioactive colloidal gold. Table 2 presents a summary of sex, age, sites of tumor origin, pertinent descriptive medical data, the method of treatment, duration of survival and results. There were 16 females and 1 male. This reflects the high incidence of malignant peritoneal effusions from ovarian and breast tumors. The diagnoses are interesting: no site of tumor origin could be determined for the single male patient. Among the females, peritoneal carcinomatosis originated from tumors of the ovary in 10, the breast in 2, the fallopian tube in 1, the lung in 1 and an unidentified site in 1. One patient was considered to have a mesothelioma on the basis of repeated cytologic studies of fluid along with her clinical course, but without biopsy since no laparotomy was done. The ages varied between thirty-seven and eighty-three years. In all but 1 patient malignant cells were identified in samples of fluid; 1 patient seemed to have certain carcinomatosis on the basis of clinical course and examination although repeated studies of paracentesis fluid by Papanicolaou technic and by cell block and section failed to show tumor cells (Case 25, Table 2). A large number of medical and surgical measures had been used in therapy for these patients before gold radiation. Many had been treated with external irradiation and various homone therapies. Each case was critically considered regarding other measures to appraise accurately the effects of gold therapy. One patient (Case 27, Table 2) had pleural treatment also, and another (Case 24, Table 2) was retreated a week after initial therapy. Another patient (Case 7, Table 1), after uneventful chest treatment, had a bowel perforation during trochar introduction for diagnostic study of ascites; a fecal fistula resulted and did not unduly complicate the patient's course although no abdominal treatment was ultimately given. The cases are divided into four groups for analysis.

Determinate Group 1 (Table 2) is made up of 2 patients who appeared to have had complete control of their ascites. One of these (Case 15), a fifty-six-year-old woman, lived for only two months with extensive metastasis from a pulmonary carcinoma but during that time experienced complete relief from her ascites. The other (Case 16), a sixty-seven-year-old woman, was still living after fifteen months with a presumed mesothelioma and with complete control of a previously extensive ascites. Determinate Group 2 includes 3 patients whose ascites was controlled so that further paracentesis was not required, but who received no useful palliation from their total disease by the gold radiation. These patients lived for three to eight months but remained entirely invalided, with rapidly progressing, downhill courses and persistence of pain and other symptoms of disability. All 3 had ovarian carcinomatosis and seemed to be poor candidates for therapy in retrospect because of the advanced state of solid tumor growth at the time of treatment.

Determinate Group 3 consists of 7 patients who received no useful palliation or control of their re-accumulating ascites. Survival ranged from two to ten months, but no one seemed to be specifically aided by gold radiation.

Cases 27 through 31 are considered to fall into indeterminate Group 4 so far as the effect of intraperitoneal gold radiation on the malignant effusions is concerned. The first 4 of these were moribund at the time of treatment and died in too short a time for any change to be appraised. The fifth showed no evident control of re-forming ascites by the gold radiation; her long survival was due to other measures.

*One may use the method of Chamberlain et al. (modified from Marinelli, Quimby and Hine[14]) for calculating tissue radiation on a plane surface delivered by a beta-emitting substance with the characteristics of radioactive gold. A tissue dosage of 60,500 rep (roentgen equivalent physical) is delivered if one employs 92 millicuries — as shown in Figure 1 — and the pleural surface is an estimated 1376 sq. cm. Thus, although half the radiation effect is lost in the direction of the fluid side of the plane interface, a destructive tissue dosage that is certainly locally cancerocidal is employed. Peritoneal surfaces present much greater areas, and tissue effects are correspondingly much less.

TABLE 2. *Results of Au^{198} Treatment of Peritoneal Effusion Due to Malignant Tumors.*

Case No.	Patient	Sex	Age	Pathological Diagnosis	Medical History	Treatment	Survival	Result
			yr.				mo.	
Determinate Group 1 (benefit)*:								
15	N.G.	F	56	*Pulmonary adenocarcinoma* (specimen, cytology of fluid & cell block)	Extensive metastases 1 yr. after pulmonary lobectomy (abdomen, liver & mediastinum)	Trochar, 107 mc.	2	Ascites relieved; death from other metastases.
16	B.K.	F	67	?*Mesothelioma* (cytology of fluid only)	Patient has nodular pelvic tumor growth; x-ray treatment to abdomen did not help ascites.	Trochar, 102 mc.	15†	Ascites completely cleared; slow weight loss & progression of solid tumor growth.
Determinate Group 2 (doubtful benefit)‡:								
17	E.R.	F	57	*Ovarian carcinoma* (specimen)	Pelvic tumor excised 9 yr. before; 1 yr. of deterioration despite x-ray therapy; 7 paracenteses in 8 wk.	Laparotomy, catheters, 85 mc.	3	Ascites controlled although deterioration continued & patient had no useful palliation
18	C.S.	F	57	*Ovarian carcinoma* (specimen)	Total hysterectomy 8 mo. before; severe abdominal pain associated with ascites; 1 pretreatment paracentesis.	Trochar, 91 mc.	8	Ascites persisted in smaller amount; severe pain persisted; no real benefit for patient.
19	D.M.	F	48	*Ovarian carcinoma* (specimen)	Bilateral oöphorectomy for tumor 10 yr. before	Laparotomy, catheters, 90 mc.	3	Ascites controlled; steady downhill course continued.
Determinate Group 3 (no benefit)§:								
20	F.V.	F	41	*Fallopian-tube carcinoma* (specimen)	Ascites & pain 1 yr. after hysterectomy for favorable lesion	Trochar, 107 mc.	6	No fluid control or useful palliation
21	R.D.	F	58	*Ovarian carcinoma* (cytology of fluid)	Disabling ascites; 4 pretreatment paracenteses.	Trochar, 102 mc.	8	Post-treatment paracenteses required; no benefit.
22	M.S.	F	44	*Ovarian carcinoma* (specimen)	Diagnosis made at earlier laparotomy; total hysterectomy at time of gold treatment; many pretreatment paracenteses.	Laparotomy, catheters, 90 mc.	6	No fluid control or benefit
23	H.M.	F	69	*Ovarian carcinoma* (specimen)	Ovarian tumor resected 7 yr. before; many pretreatment paracenteses.	Laparotomy, catheters, 90 mc.	10	Clinical progression; no fluid control.
24	E.C.	F	56	*Ovarian carcinoma* (specimen)	Bilateral ovarian tumors excised 2 yr. before; irradiation for ascites without benefit.	Trochar, 90 mc.; then 92 mc. after 1 wk.	2	No control of fluid; patient's poor condition did not improve.
25	S.D.	F	83	?*Carcinoma* (negative cytology cell block & clinical diagnosis of abdominal carcinomatosis)	Progressive inanition & ascites; no origin of presumed tumor established.	Trochar, 89 mc.	2	Disease altered but little; ? decrease of degree of ascites.
26	M.W.	F	61	*Ovarian carcinoma* (biopsy)	Ovarian carcinoma excised 3 mo. before; ascites appeared not relieved by irradiation.	Laparotomy, catheters, 100 mc.	3	No relief
Indeterminate Group 4¶:								
27	C.W.	M	63	*Pleural & peritoneal carcinoma* (biopsy); ?origin.	Patient ill for 3 mo., with bilateral pleural & peritoneal effusions; biopsy at laparotomy; no site of origin identified.	Laparotomy, catheters, 100 mc. (previous pleural treatment on right)	2/4	Rapid deterioration of moribund patient; survival too short to evaluate response.
28	P.I.	F	61	*Breast carcinoma* (biopsy)	Patient ill only 1 mo.; study showed liver, peritoneal & bony metastases.	Trochar, 98 mc.	<1 (3 days)	Patient moribund when treated
29	E.W.	F	57	*Ovarian carcinoma* (biopsy)	Diffuse tumor at time of exploration; no benefit from x-ray treatment to abdomen or nitrogen mustard; no paracenteses done.	Trochar, 100 mc.	<1 (4 days)	Patient moribund when treated
30	E.N.	F	51	*Ovarian carcinoma* (specimen)	Oöphorectomy for tumor 10 mo. before; x-ray treatment; 3 paracenteses each wk. before gold treatment.	Trochar, 103 mc.	3/4	No change in fluid; death too early for evaluation.
31	E.D.	F	37	*Breast carcinoma* (specimen)	Mastectomy 7 yr. before; late recurrence with bony, peritoneal, & liver metastases; x-ray treatment, then male hormone; surgical castration; gold radiation, then cortisone, salt restriction & improvement.	Laparotomy, catheters, 87 mc.	10†	Tumor regressing & fluid entirely controlled; improvement most probably due to hormone therapy.

*Apparent benefit from Au^{198} treatment.
†Patient living.
‡Ascites relieved, but no useful palliation of total problem.
§No benefit from Au^{198} treatment.
¶Death from far advanced disease too soon for evaluation, or improvement explained by other treatment.

Thus, among 17 patients treated for malignant peritoneal effusions, 5 either died too soon for results to be appraised or may have benefited from some other treatment, 2 demonstrated good control of their tendency to re-form ascites, 3 showed some improvement in ascites formation but had no truly useful palliation, and 7 experienced no benefit from the treatment. The 8 patients comprising Groups 2 and 4 and perhaps some of the patients in Group 3 were not ideal candidates for the therapy. A study of these cases suggests that duration of survival alone cannot be considered the equivalent of useful palliation; this may explain a discrepancy in results in this group as compared with the 50 per cent benefit reported by most other authors.

Pleural Effusions

Fourteen patients with malignant pleural effusions were treated. Table 1 presents descriptive data concerning these; the dose of radioactive gold ranged from 69 to 106 mc. There were 11 females and 3 males, and again this reflected the high incidence of serous-cavity spread with effusion of carcinomas of the ovary and breast. Eight lesions originated from the breast, and 3 from the ovary. The 3 males presented Hodgkin's disease of the lung and a pulmonary carcinoma, and the patient (Case 12, Table 1) who had carcinomatosis of the peritoneum and pleural cavity of undetermined origin. Two patients had bilateral effusions and bilateral treatment, and the 1 patient mentioned also had peritoneal treatment (Case 12, Table 1). There were no accidents associated with administration of the gold although, in 1 case, there was apparently perforation of the lung with a needle tip and instillation of material, which was coughed up and which spilled over into the opposite lung as evidenced by post-treatment monitor observation. This caused a radiation pneumonitis, which was controlled by cortisone treatment. The major part of that therapeutic dose remained on the side of the effusion and produced a long-term good result (Case 2, Table 1).

A determinate Group 1 of 8 patients exhibited good results with control of fluid so that further thoracenteses were not required for periods ranging between two and twenty-seven months. All these had positive cytologic examination of thoracentesis fluid, and in all cases the palliative benefit of this therapy was quite striking. Five had carcinomas originating in the breast, 2 in the ovary, and 1 in the lung.

A determinate Group 2 showed no benefit. Here, 2 patients with breast carcinoma died two and three months after treatment, but in 1 case additional thoracenteses were required. The other patient was disabled by reaccumulated fluid.

Four patients were considered indeterminate in that all died within three weeks of treatment, and the results could not be appraised (Group 3).

Discussion

It is notable that among the 31 patients described above no condition resembling radiation sickness was seen. This has been the usual reported experience and must be related to the absence of deep visceral irradiation (such as the liver or the mucous membrane of the gastrointestinal tract) that seems to precede the condition. Bone-marrow depression has not been seen in this series, and a study by Copeland[15] has failed to disclose examples of such an effect as has been reported by Botsford et al.[16] No incidental radiation injury to personnel concerned with care of any of these patients occurred, and undesirable adventitious contamination of dressings, bedclothes and the like has been minimal. Treatment of the chest cases is essentially uncomplicated. Peritoneal treatment seems best administered through catheters placed during laparotomy for many reasons. In this series, gold-contaminated peritoneal fluid leaked out through one trochar site and produced inconvenience; an accidental bowel perforation has already been discussed. In addition cases of apparent introduction of the radioactive material into isolated loculi in the peritoneum, with resulting necrosis of the bowel and bladder, have been reported.[17] These complications can all be avoided by laparotomy and direct placement of catheters for gold instillation. Other benefits may include establishing a certain diagnosis, especially regarding the problem of complicating liver lesions, performing a thorough peritoneal toilet with maximum relief of ascites by aspiration of fluid and the clotted masses seen in the pseudomyxomatous state produced by some ovarian tumors. Other surgical steps may be taken, such as ovariectomy in breast cancer.

Establishing a certain tissue diagnosis to substantiate disseminated cancer as the cause of an effusion seems essential. Cardiac, renal and hepatic disease may be associated with fluid retention in serous cavities. This may be difficult to evaluate when there is metastasis to the liver and on the peritoneal surfaces and when liver-function studies may be markedly altered. Finding malignant cells in the recovered fluids may be difficult when prior irradiation has been given, but identification of cells either by the Papanicolaou technic or by cell block should almost always be possible otherwise. We have observed disappearance of recognizable tumor cells after therapy with radioactive gold. In selection of patients it seems clear that the moribund state must usually contraindicate treatment.

Although the number of patients treated may not be sufficiently large to reveal differences, no single tumor in the series presented seems to offer a more or less favorable prognosis than any other. Also, among these patients we can discern no difference in prognosis between the group with a short history of seemingly rapid progress of disease and that with diagnosis

first made many years before. Occasional post-treatment fluid aspirations have been required, and this in itself does not indicate a poor result. In 1 patient (Case 6, Table 1), three post-treatment thoracenteses were required during two months, and then the patient's chest remained dry until death five months later.

The amount of radiation given in this series was not as great as has been employed by some.[18] Among many unanswered questions are those concerning optimal dosage, the usefulness of retreatment of the same area and the possible value of combined therapy with nitrogen mustard substances.[19] When one considers the great difference in surface area contained within the peritoneal cavity as compared to a single pleural cavity, the need for much larger amounts of radioactive substance in the peritoneal treatment is suggested.

The ideal patient for therapy of malignant effusion with radioactive colloidal gold appears to be one whose chief problem is the accumulation of fluid in the chest or abdomen but who is not severely debilitated or approaching a terminal state because of other effects of his disease. This seems especially important so far as ascites is concerned; disturbed bowel function in patients with carcinomatosis arising from the ovary appears to be a grave prognostic sign. For malignant pleural effusions, the aged woman who demonstrates local chest-wall recurrence along with metastatic spread to the pleura on the same side with an effusion, two or three years after initial surgery for breast cancer, is perhaps the best candidate for this treatment. A patient who is well oriented, with some knowledge of the diagnosis, and who understands what is being attempted and what the problems and prognosis may be will usually be best prepared psychologically. This is particularly important with the use of radioactive isotopes since it may be difficult to avoid raising false hopes either in the patient or in the family. When one considers the great improvement in long-term survival after surgery for ovarian carcinoma when "prophylactic" radiation is given to the pelvis and abdomen early in the patient's course, as reported by Marks and Wittenborg[20] and by Allan and Hertig,[21] the early use of radioactive gold to deliver its relatively large local radiation onto surfaces within the peritoneal cavity is appealing. Recently reported studies showing how commonly cancer cells can be demonstrated by cytologic technics in peritoneal washings from even the most favorable cases of ovarian carcinoma[18] also suggest the importance of early therapy to prevent later recurrence. We have had no experience with this use of the material, and many years' observation will be required to ascertain its efficacy in that role.

Summary and Conclusions

The use of radioactive colloidal gold (Au^{198}) for therapy of malignant pleural and peritoneal effusions is discussed.

Results of treatment of 31 patients at the New England Deaconess Hospital are presented. Of 17 malignant peritoneal effusions, 12 were considered to be determinate cases; effective control of ascites was achieved in 2, some control of fluid was observed in 3 others without much benefit in total, and no benefit occurred in the remaining 7. Of 14 cases of pleural effusions secondary to metastatic cancer, 10 were considered to be determinate; 8 patients showed good results with effective control of their pleural effusions whereas 2 did not. With the dosages and technic reported, results were distinctly better in the treatment of pleural metastases.

Selection of patients for treatment and the technic and safety of this are considered.

Radioactive colloidal gold (Au^{198}) offers a safe, predictable and useful therapy for malignant pleural effusions. Results of treatment for malignant peritoneal effusions are less favorable. Usefulness of this material for "prophylactic" radiation in favorable cases of ovarian carcinoma is predicted.

We are indebted to Dr. Shields Warren for guidance and planning of this program and to Miss Egilda DiAmicis, S. B., and Miss Dorothy Blanchard, R. N., for painstaking technical assistance.

References

1. Sheppard, C. W., Wells, E. B., Hahn, P. F., and Goodell, J. P. Studies of distribution of intravenously administered colloidal sols of manganese dioxide and gold in human beings and dogs using radioactive isotopes. *J. Lab. & Clin. Med.* **22**:274-286. 1947.
2. Williams, G. Z., Stanton, A. C., Jamison, R. M., and Williams, J. T. Distribution of radioactive gold colloid in rats, mice, and transplanted mouse tumors. *South. M. J.* **43**:1031-1038. 1950.
3. Sheppard, C. W., Furth, J., and Wish, L. Fate of gold colloids introduced into circulation of mouse. *Federation Proc.* **9**:343, 1950.
4. Sheppard, C. W., Jordan, G., and Hahn, P. F. Disappearance of isotopically labeled gold colloids from circulation of dog. *Am. J. Physiol.* **164**:345-350. 1951.
5. Hahn, P. F., Goodell, J. P. B., Sheppard, C. W., Cannon, R. O., and Francis, H. C. Direct infiltration of radioactive isotopes as means of delivering ionizing radiation to discrete tissues. *J. Lab. & Clin. Med.* **32**:1442-1453. 1947.
6. Zeidman, I., Copeland, B. E., and Warren, S. Experimental studies on spread of cancer in lymphatic system. II. Absence of lymphatic supply in carcinoma. *Cancer* **8**:123-127. 1955.
7. Allen, W. M., Sherman, A. I., and Bonebrake, M. Use of radioactive gold combined with radical abdominal hysterectomy and pelvic lymph node dissection in treatment of carcinoma of cervix. Presented at Second National Cancer Conference, Cincinnati, Ohio, March 3-5, 1952.
8. Seaman, W. B., and Powers, W. E. Studies on distribution of radioactive colloidal gold in regional lymph nodes containing cancer. *Cancer* **8**:1044-1046, 1955.
9. Ellis, F., and Oliver, R. New technique for treating papillomatosis of bladder with colloidal gold and some unusual applications of tantalum wire. In *Radioisotope Conference: Proceedings of the second conference, Oxford, 19-23 July, 1954: Sponsored by the Atomic Energy Research Establishment, Harwell.* 2 vol. Vol. 1. *Medical and Physiological Applications.* Edited by J. E. Johnston et al. 418 pp. New York: Academic Press, 1954.
10. Overholt, R. E. Unpublished data.
11. Meneely, G. R., Kory, R. C., Auerbach, S. H., and Hahn, P. F. Distribution of radioactive colloidal gold following intrapulmonary administration. *Federation Proc.* **10**:365, 1951.
12. Müller, J. H., and Rosier, P. H. New method for treatment of cancer of lungs by means of artificial radioactivity (Zn^{62} and Au^{198}): first experimental and clinical studies. *Acta radiol.* **35**: 449-468. 1951.
13. Rose, R. G., Osborne, M. P., and Stevens, W. B. Intracavitary administration of radioactive colloidal gold. *New Eng. J. Med.* **247**:663-667. 1952.
14. Marinelli, L. D., Quimby, E. H., and Hine, G. J. Dosage determination with radioactive isotopes. II. Practical considerations in therapy and protection. *Am. J. Roentgenol.* **59**:260-281, 1948.
15. Copeland, B. E. Unpublished data.
16. Botsford, T. W., Wheeler, H. B., Newton, R. A., and Jaques, W. E. Hypoplasia of bone marrow associated with radioactive colloidal gold therapy. *J.A.M.A.* **151**:788-791, 1953.
17. Nolan, J. F. In discussion of Allen, Sherman and Bonebrake.[7]

18. Keettel, W. C., and Elkins, H. G. Experience with radioactive colloidal gold in treatment of ovarian carcinoma. *Am. J. Obst. & Gynec.* **71**:553-568, 1956.
19. Weisberger, A. S., Levine, B., and Storaasli, J. P. Use of nitrogen mustard in treatment of serous effusions of neoplastic origin. *J.A.M.A.* **159**:1704-1707, 1955.
20. Marks, J. H., and Wittenborg, M. H. Results of treatment of carcinoma of ovary with data on age incidence of this disease. *Surg., Gynec. & Obst.* **87**:541-545, 1948.
21. Allan, M. S., and Hertig, A. T. Carcinoma of ovary. *Am. J. Obst. & Gynec.* **58**:640-653, 1949.

CLINICAL APPLICATION OF GASTRIC CYTOLOGY

ROBERT E. CROZIER, M.D.,* MARGARET MIDDLETON,† AND JOHN R. ROSS, M.D.‡

BOSTON

IN the last ten years, much interest has been shown in gastric cytology as a useful clinical aid. This procedure is not new, however: a number of German investigators[1] at the turn of this century reported good results utilizing a technic devised by Ehrlich. Direct examination of unstained and unfixed gastric-aspiration material was made. One investigator[2] obtained an accuracy of 86 per cent in 37 patients with gastric cancers. With the advent of diagnostic roentgenology and endoscopy in the succeeding decades, this technic of cell diagnosis fell into disuse. Papanicolaou,[3] in 1946, revived interest in the field of gastric cytology by application of a staining method that he had devised five years previously for the diagnosis of uterine and cervical cancer.[4] The results of his initial attempts in gastric cytology were not good, however, since he obtained an accuracy of only 37 per cent in 27 gastric cancers. It was evident to early investigators that one of the major problems in gastric cytology was the rapid cell degeneration observed in aspiration material. This degeneration is more rapid than that observed in other organs and is probably due to the action of acid-pepsin secretion on the exfoliated cells. Therefore, subsequent studies have been directed at technics whereby cell degeneration is minimized by rapid processing of gastric-mucosa specimens, and the quantity of cellular material is increased by abrasion.

In 1948 Ulfelder, Graham and Meigs,[5] using normal saline lavage and rapidly processing the material obtained, described good results. This group reported an accuracy of 85 per cent in 14 cases of gastric carcinoma. After introduction of the saline solution through a stomach tube they suggested rotating the patient from side to side in the supine position so that all surfaces of the stomach were adequately lavaged.

Abrasive cytology was introduced in 1950 by Panico et al.,[6] who proposed the use of a double-lumen tube on the end of which was an inflatable balloon covered by a fine mesh. The inflated balloon was used to abrade the mucosa of the stomach and thereby to promote exfoliation of cells. First attempts with this technic resulted in an accuracy of 82.4 per cent. Rubin et al.[7] designed a similar balloon, which was considered more certain of reaching antral and prepyloric lesions. It had a weighted mercury tip distal to the balloon that could be visualized fluoroscopically to pass into the proximal duodenum; one could be assured under these conditions of the balloon's antral position. In 1953 Ayre[8] introduced another abrasive instrument known as the Ayre brush. This instrument consisted of a plastic tube encasing a cable on the end of which was a small, soft, bivalved brush made of boar's hair. The brush was maneuvered to the site of the lesion, and by rotation of the cable the involved portion of the stomach was selectively swept. Smears were then made from material collected by this procedure. Ayre reported an accuracy of 78 per cent in 14 cases of gastric cancer in which the brush was used.

Two mucolytic agents, papain[9] and chymotrypsin,[7] were suggested in 1951 and 1953 respectively as valuable additions to gastric-lavage technics. Indications for the use of these agents arose from their mucolytic effects upon the gastric mucosa, thereby theoretically releasing entrapped tumor cells for cytologic analysis.

More recently, investigators have been carrying out combined cytologic studies, gastric abrasion and gastric lavage.

SELECTION OF CASES

The present study was begun in January, 1955, by Ross, Carvalho and Middleton[10] at the Lahey Clinic. Inpatient studies were made at the New England Deaconess and New England Baptist hospitals. A few outpatients were studied at the Lahey Clinic. The present report covers the entire series of patients on whom the combined abrasion and lavage procedures have been performed in the last sixteen months. Although we were especially interested in obtaining patients thought clinically to have a malignant lesion, we accepted all patients in whom any type of gastric disease was suspected, particularly when neoplasm was questioned.

In the analysis of 122 patients investigated final diagnosis was ascertained by observation of response to medical therapy or by surgical exploration. The specimens obtained from 5 additional patients were unsatisfactory principally because insufficient material was delivered for microscopical analysis. These data were not included in the statistics.

*Member, Department of Gastroenterology, Lahey Clinic.
†Cytologist, Department of Pathology, New England Deaconess Hospital.
‡Member, Department of Gastroenterology, Lahey Clinic.

Technic

A combined procedure of gastric abrasion and gastric lavage was performed in all 122 patients. Abrasion was obtained with the Ayre[11] brush under fluoroscopic control. Buffer acetate, to which a mucolytic agent (chymotrypsin) was added, served as the vehicle for gastric lavage in the first 100 patients. In the last 22 patients physiologic saline solution alone was used. In a number of patients the lavage immediately preceded the abrasion; in others the reverse procedure was employed. We found no significant difference in the microscopical results by altering the order of procedure.

Various types of gastric tubes were used, and for ease of passage as well as efficient aspiration, we found the Ewald evacuator superior (this tube has a large rubber bulb that permits vigorous gastric lavage, and we believe that the effort exerted in performing the lavage is an important factor in the recovery rate of exfoliated cells). After the stomach tube had been inserted the patient was placed in the supine position and rotated from side to side while the operator carried out the lavage.

Patients were required to fast for eight to twelve hours before instrumentation, and we learned that any degree of pyloric obstruction was a contraindication to performance of these tests. Nembutal was given orally the night before and on the day of the procedure. Morphine and atropine were given hypodermically half an hour before the test. Pontocaine (2 per cent), spray or gargle, was found useful as a local anesthetic in facilitating instrumentation. Since we believe that establishing rapport with the patient is an important factor in the success of these tests, all patients were interviewed the day before the procedure, and the tests to be conducted the following morning were briefly described. In this way patient co-operation was enhanced, and apprehension was reduced to a minimum.

Lavage specimens were immediately transferred to iced containers and centrifuged within ten minutes. Three smears were prepared from the centrifuged specimens and were placed immediately in equal parts of 95 per cent alcohol and ether for fixation. Three glass slides were similarly prepared from the brush specimen (Fig. 1).

Method of Reporting

We have adopted and abbreviated a system of reporting cytologic diagnoses as suggested by Papanicolaou. The Papanicolaou system is cumbersome and contains equivocal reports, which are of no real value to the clinician. For practical purposes, therefore, only Classes 1 and 4 have clinical usefulness. This system is as follows:

Class 1 — absence of abnormal or atypical cells.

Class 2 — atypical cells present, *not* suggesting neoplasm.

Class 3 — cells with abnormal features, suggestive but not diagnostic of neoplasm.

Class 4 — tumor cells present.

Results

The present analysis combines the results of surgical treatment, follow-up clinical visits, roentgenograms and correspondence. This project has been in effect only sixteen months, and this interval may not be sufficiently long for an accurate follow-up study. In cases in which surgical therapy was used we have obtained an immediate definitive evaluation of this study, and thus far we have been able to follow closely the nonoperated patients. All malignant lesions reported were proved at the time of operation.

Figure 1. *Photomicrograph, Demonstrating Tumor Cells Characterized by Variability in Size and Staining Quality, Increased Density of the Nuclei, Vacuolization of Cytoplasm and Disposition between Cytoplasmic and Nuclear Mass (X600).*

The over-all accuracy in both malignant and benign lesions (Table 1) was 90 per cent. As reported by other investigators, a greater degree of accuracy was obtained in patients with benign than in those with malignant lesions.

At times it may be difficult or impossible to differentiate malignant and benign gastric lesions by roentgenologic studies, and this is borne out by the figures in Table 1. A correct diagnosis was made from x-ray examination in only 64 of these 93 pa-

tients with benign lesions. In the remaining 29 benign lesions, 15 of which were confirmed by operation, a suspicion of cancer was raised or a diagnosis of cancer was incorrectly made from the roentgenogram. On the other hand 90 benign lesions in this group (97 per cent) were correctly diagnosed by cytology studies as benign. There was only 1 false-positive cytologic report of tumor cells, and this was in a man with multiple polyposis of the stomach. No malignant focus was found in any of the polyps histologically examined.

TABLE 1. *Accuracy* of Cytologic and X-Ray Studies of 122 Patients with Benign and Malignant Lesions.*

GROUP	PATIENTS STUDIED	OVER-ALL ACCURACY OF CYTOLOGIC STUDIES		OVER-ALL ACCURACY OF ROENTGENOGRAM	
		NO.	PERCENTAGE	NO.	PERCENTAGE
Benign lesions	93	90	96	64	69
Malignant lesions	29	20	69	21	70
Over-all accuracy			90		70

*Relative accuracy in malignant lesions from January 1, to July 1, 1955 (13 patients studied), 38% & July 1, 1955, to April 1, 1956 (16 patients studied), 94%.

Diagnosis of malignant lesions by exfoliative cytology compared favorably with the rate of accuracy by x-ray examination (Table 1). False-negative reporting, however, was higher by cytology (8 patients) than by roentgenogram (4 patients). Yet there were considerably fewer equivocal reports by cytologic study (1 patient) than by roentgenologic study (4 patients). In 4 cases in which benign or equivocal diagnoses were made by x-ray examination cytologic reports were positive for tumor, and in each case a malignant lesion was confirmed at operation. Four patients in our series had malignant lymphomas, and in 2 of these, lymphoma cells were identified in cytologic smears.[12]

We were fortunate in obtaining tumor cells in a patient with an early, unsuspected gastric cancer. This seventy-year-old man was in excellent health until two weeks before admission, when he experienced hematemesis. A crater along the lesser curvature was shown on x-ray examination to have many features of a benign lesion. It was decided to give the patient a course of medical therapy, until cytology studies were made and tumor cells were reported. Operation was performed immediately, and a small, easily resectable malignant ulcer was found.

It has been encouraging to us that between July 1, 1955, and April 1, 1956, we have had an accuracy of 94 per cent in the cytologic diagnosis of 16 malignant lesions. This represents an improvement in accuracy of almost three times that noted for the initial period (January 1 to July 1, 1955) of this study. As pointed out below, we believe that this greater accuracy is due in part to more vigorous efforts in the gastric lavage and a generally improved collection system that comes with experience (Table 1).

Results to date with the Ayre brush have not been encouraging. The results of a carefully performed gastric lavage using physiologic saline solution have proved to be more reliable than those obtained with the Ayre brush.

DISCUSSION

It is generally agreed that successful cytologic interpretation of gastric specimens is dependent on the speed and care with which the cellular material is collected and processed. Gastric lavage was performed by one of our group (R.E.C.), and the "brush test" by another (J.R.R.). The average time expended in obtaining and centrifuging each gastric-lavage specimen was thirty-five minutes, whereas the "brush test" took only twenty minutes to perform. The combined procedure, therefore, took less than an hour.

Cytologic analysis of all cases was performed by the third member of our group (M.M.). The clinical impression was purposely withheld, so that cytologic diagnosis was made on a purely objective basis.

Using the rapid-collection technics described above, we have seen little evidence of cell degeneration. We have, however, encountered considerable extraneous cellular material from the esophagus, nose, throat and, at times, the lungs. At present we have no solution for the elimination of these cells. In our brief experience, the stage of the gastric cancer does not alter the possibility of obtaining a positive cytologic diagnosis. Cancer involving an extensive portion of the stomach, however, provides smears with a greater abundance of tumor cells.

As mentioned previously, abrasion was obtained by the Ayre brush in all cases here reported. The antral abrasive balloon has been given a trial by one of us (J.R.R.) and reported elsewhere[10] but was abandoned because it was found to take too much time and to be too cumbersome. The Ayre brush has many advantages: ease of passage, good quality of specimens, less time than other abrasive instruments and, in our experience, fluoroscopic control. The brush has some objectionable features, however, the chief of which is the difficulty of ensuring the sweeping of the involved portion of the stomach. Another adverse feature is the possible failure of maneuvering the instrument to the antrum in a high transverse stomach. To date we have had no serious complication from the use of the brush. However, it should probably be reserved for extensive lesions where one is sure that the diseased area is being swept.

A far simpler, less traumatic and, in our opinion, more reliable procedure is gastric lavage with physiologic saline solution. It should be emphasized that cell collections should be made only by well trained personnel, for good results depend on the care and interest taken in the collection technic. We have

demonstrated to our satisfaction that addition of one of the mucolytic agents (chymotrypsin) to the solution does not materially increase the quantity or improve the preservation of cancer cells. Likewise, results have not been improved by the use of an acetate buffer, and we discovered that this solution has the objectionable feature of forming a sediment on standing, necessitating straining before being used. Physiologic saline solution seems to be adequate for cell preservation, but further evaluation of this vehicle will be necessary.

Negative cytologic reports should be ignored when a gastric cancer is strongly suspected on clinical grounds. If our present rate of accuracy (94 per cent) remains constant, however, a negative report should have progressively greater value. There were several patients who on clinical grounds appeared to have malignant lesions but in whom cytologic studies were negative for tumor cells. The benign nature of these lesions was proved at operation.

Summary and Conclusions

The accuracy of results in gastric cytology is dependent upon the careful, rapid collection and processing of the material by well trained, interested personnel.

Gastric lavage with physiologic saline solution is a simple, comparatively reliable method for cytologic examination. Abrasive technics, in our hands, have not proved to be as practical or reliable as gastric lavage.

It appears to us that the circumstances in which gastric cytology is most useful are to substantiate the clinical impression of a benign lesion, to enhance the clinical impression of a malignant lesion and, on occasion, to diagnose an early, unsuspected gastric cancer.

Although gastric cytologic study is not considered a substitute measure for gastroscopy or roentgenography of the stomach we believe that as experience accumulates with this method of investigation, its position as a reliable supplement to other forms of investigation of gastric disease will become increasingly apparent.

This study contributed positively to the diagnosis of cancer in 4 cases later confirmed by operation in which the x-ray diagnosis was benign disease or was equivocal. But more frequently it strengthened a clinical impression of a benign lesion, resulting in continued conservative management and the avoidance of surgery without harm to the patient. A prolonged follow-up study of these patients will be necessary before more definitive conclusions can be presented.

It is hoped that gastric cytology will continue to be actively supported so that more valuable statistical information may become available.

References

1. Frishman, R. L., and Gorin, M. G. Diagnostic significance of examination of gastric washings in patients suspected of cancer of stomach. *Klin. med.* **20**:59-67, 1942.
2. Marini, G. Ueber die Diagnose des Magenkarzinoms auf Grund der cytologischen Untersuchung des Spülwassers: eigene Beobachtungen über den normalen und pathologischen Zelleninhalt des Magens. *Arch f. Verdauungskr.* **15**:251-267, 1909.
3. Papanicolaou, G. N., Cooper, W. A., and Ledyard, L. C. Cytology of gastric fluid in diagnosis of carcinoma of stomach. Presented at the Conference on Gastric Cancer of the Gastric Cancer Committee of the National Advisory Cancer Council, Chicago, December 5-6, 1946.
4. Papanicolaou, G. N., and Traut, H. F. *Diagnosis of Uterine Cancer by the Vaginal Smear*. 47 pp. New York: Commonwealth Fund, 1943.
5. Ulfelder, H., Graham, R. M., and Meigs, J. V. Further studies on cytologic method in problem of gastric cancer. *Ann. Surg.* **128**: 422-424, 1948.
6. Panico, F. G., Papanicolaou, G. N., and Cooper, W. A. Abrasive balloon for exfoliation of gastric cancer cells. *J.A.M.A.* **143**: 1308-1311, 1950.
7. Rubin, C. E., Massey, B. W., Kirsner, J. B., Palmer, W. L., and Stonecypher, D. D. Clinical value of gastrointestinal cytologic diagnosis. *Gastroenterology* **25**:119-138, 1953.
8. Ayre, J. E., and Oren, B. G. New rapid method for stomach-cancer diagnosis: gastric brush. *Cancer* **6**:1177-1181, 1953.
9. Rosenthal, M., and Traut, H. F. Mucolytic action of papain for cell concentration in diagnosis of gastric cancer. *Cancer* **4**:147-149, 1951.
10. Ross, J. R., Carvalho, P. J., and Middleton, M. Progress report with reference to cell diagnosis in gastric lesions. *Lahey Clin. Bull.* **9**:167-173, 1955.
11. Ross, J. R., and Crozier, R. E. Technique of brush test for gastric cytology. *S. Clin. North America* **36**:649-652, 1956.
12. Rubin, C. E., and Massey, B. W. Preoperative diagnosis of gastric and duodenal malignant lymphoma by exfoliative cytology. *Cancer* **7**:271-288, 1954.

THE EFFECT OF PREGNANCY ON GASTRIC SECRETION*

W. A. Gryboski, M.D.,† and H. M. Spiro, M.D.‡

NEW HAVEN, CONNECTICUT

PREGNANCY is said to alleviate the symptoms of peptic ulcer, according to numerous clinical reports.[1-5] The availability of an indirect measure of gastric secretion by the blood pepsin method[6,7] offered an excellent opportunity for study of the effect of pregnancy on gastric secretion. Blood pepsin levels usually parallel gastric pepsin levels and are taken to be a reflection of gastric secretory activity. This study suggests that the alleviation of duodenal ulcer by pregnancy may be related more to diet and care than to the physiologic events.

*From the Department of Internal Medicine, Yale University School of Medicine.

This work, which was carried out as part of the fourth-year student thesis of Dr. Gryboski, was supported in part by grants from the United States Public Health Service (C 2578), the Fluid Research Fund of Yale University and the American Cancer Society.

†Surgical intern, Grace-New Haven Community Hospital.

‡Assistant professor of medicine, Yale University School of Medicine; associate physician, Grace-New Haven Community Hospital.

Method

Twenty-one pregnant women, from eighteen to forty-two years of age, were studied in the prenatal

clinic of the Grace-New Haven Community Hospital. No patient had symptoms or a past medical history of peptic ulcer. It was possible to get consecutive monthly blood pepsin levels on 13 of the 21 women only from the seventh month of gestation to delivery and during the post-partum period up to one hundred and forty days after delivery. This smaller group of the 13 women ranged in age from nineteen to forty-two. Blood samples were drawn at the routine monthly visits and biweekly during the last two months of pregnancy. The plasma was assayed at once in duplicate by the previously reported method.[6,7]

ject is represented by more than 1 determination in any month. The mean monthly values in Table 2 do not vary from the monthly values in Table 1 by more than 5 pepsin units.

Table 3 presents the individual and mean values one day, forty-two days, and one hundred and twenty to one hundred and forty days post partum. Seven of the values in the post-partum period do not fall within the normal range of blood pepsin values, 4 being above and 3 being below the accepted normal. There is a mean value of *431* units on the day after delivery. The mean value forty-two days after delivery is noted to have dropped back to *381* units.

TABLE 1. *Pepsin Units during Various Months of Pregnancy.*

PEPSIN UNITS						
3D MO.	4TH MO.	5TH MO.	6TH MO.	7TH MO.	8TH MO.	9TH MO.
235	393	342	298	418	378	368
400	250	414	288	330	298	435
294	285	298	330	348	333	368
272	200	389	273	348	425	495
325	316	233	280	443	280	330
333	278	237	315	355	290	400
295	350	273	300	265	338	368
		363	243	308	412	345
av. 299	av. 298	305	365	185	350	393
No. 7	No. 7	260	373	580	340	120
		435	220	260	210	350
			280	397	325	487
		av. 329	385	383	447	294
		No. 12		450	224	438
			av. 295	260	266	402
			No. 14	443	438	472
				265	465	225
				403	295	265
				378	348	410
				263	518	275
				375	308	304
				238	320	752
					453	600
				av. 346	238	463
				No. 23	375	307
						270
					av. 356	250
					No. 26	253
						340
						812
						620
						274
						224
						av. 381
						No. 34

RESULTS

A hundred and twenty-three pepsin values arranged according to the month in which they were drawn are shown in Table 1. Fourteen values in the third and fourth months and 4 during the eighth and ninth months were obtained from 18 other pregnant women chosen at random. The remaining 103 values are from the 21 original subjects. All values in Table 1 fall in the normal range of blood pepsin activity except for 6 values from 3 patients during the eighth and ninth months. The mean monthly values in Table 1 are also all within the normal range. However, a rise from a mean of *299* units in the third month to a mean of *381* units in the ninth month of pregnancy is noted.

In Table 1 some subjects are represented by more than 1 pepsin value in certain months. Table 2 lists 106 blood pepsin values from Table 1, but where 2 levels had been determined in one month, only 1 has been selected at random, so that in Table 2 no subject is represented by more than 1 determination in any month. The mean monthly values in Table 2 do not vary from the monthly values in Table 1 by more than 5 pepsin units.

Table 3 presents the individual and mean values one day, forty-two days, and one hundred and twenty to one hundred and forty days post partum. Seven of the values in the post-partum period do not fall within the normal range of blood pepsin values, 4 being above and 3 being below the accepted normal. There is a mean value of *431* units on the day after delivery. The mean value forty-two days after delivery is noted to have dropped back to *381* units. The blood pepsin level then falls off to a mean level of *331* units at one hundred and twenty to one hundred and forty days post partum.

The average mean values of Tables 1 and 3 are plotted in Figure 1. No mean value during pregnancy is higher than the mean level one day post partum.

In Table 4 these 123 blood pepsin values are divided according to trimester of pregnancy. The mean levels for the first and second trimesters are *299* units and *308* units. There is a rise in the third trimester to *361* units, reaffirming the previous suggestive rise in gastric secretory response as pregnancy progresses.

Table 5 shows the average blood pepsin values of the 13 women followed in consecutive months from the seventh month and also at one, forty-two, and one hundred and twenty to one hundred and forty days post partum. Although the consecutive monthly values varied widely in individual cases, a progressive rise was noted (though not a statistically sig-

nificant one) in the mean pepsin values from *367* units at the seventh month to *456* units on the first day post partum. After this, there was a decrease to a level of *331* units — a statistically significant decrease.

However, it is recognized that this normal value was determined from a group of normal males and females of all ages and that comparison with the present group of young women may be inaccurate.

There was no significant change in the normal

TABLE 2. *Further Breakdown of Pepsin Units during Various Months of Pregnancy.*

PEPSIN UNITS						
3D MO.	4TH MO.	5TH MO.	6TH MO.	7TH MO.	8TH MO.	9TH MO.
235	393	342	298	418	378	368
400	260	414	288	330	325	435
234	285	273	330	348	298	368
272	200	305	315	348	425	330
325	316	410	300	265	280	368
333	278	260	243	308	290	345
295	350	433	365	185	338	270
av. 299	av. 298	362	185	275	412	350
No. 7	No. 7	389	373	580	350	487
		233	220	260	580	438
		237	280	397	340	402
		298	385	383	210	225
		av. 329	273	443	224	410
		No. 12	av. 296	265	266	275
			No. 13	403	438	304
				378	465	752
				263	295	463
				375	348	270
				238	518	340
				260	308	812
				443	320	274
				av. 341	453	224
				No. 21	238	av. 386
					375	No. 22
					av. 354	
					No. 24	

DISCUSSION

Although blood pepsin closely parallels gastric pepsin activity, disproportion between gastric pepsin and acid occurs when secretion fails.[8] It is possible for the blood pepsin to be high in the presence

TABLE 3. *Blood Pepsin Units Post Partum.*

PEPSIN UNITS		
1 DAY POST PARTUM	42 DAYS POST PARTUM	120-140 DAYS POST PARTUM
345	325	286
293	308	362
418	385	208
403	313	320
495	256	175
333	363	252
300	190	432
425	400	363
287	357	260
406	310	350
292	498	340
700	287	700
765	472	av. 331
176	457	No. 13
235	675	
520	337	
324	430	
375	320	
505	505	
av. 431	322	
No. 19	392	
	av. 381	
	No. 21	

of low or normal gastric acidity. Since this phenomenon is not common the blood pepsin level as an indirect measure of gastric acid, as well as of gastric secretion, in pregnancy seems feasible. Most of the values in pregnancy and in the post-partum period were in the accepted range of normal. The mean normal of *353* units reported in a previous publication[7] was not significantly greater than the present values during the first six months of pregnancy.

levels of blood pepsin during the first two trimesters of pregnancy. The lowest blood pepsin levels occurred during the sixth month, after which there was a rise in levels from the seventh month to a maximum on the first post-partum day. This suggestive rise was seconded by the rise in blood pepsin mean values during the third trimester. The eventual decrease to the original levels of the early months of

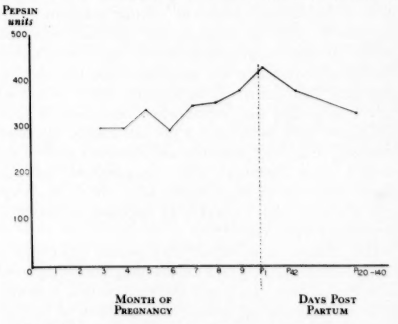

FIGURE 1. *Average Mean Values in Pregnancy. The average blood pepsin level is seen to rise with the progress of pregnancy, to reach a peak on the first post-partum day.*

pregnancy, after the post-partum peak, suggests an increase in gastric secretion during the last trimester.

A contribution of the gastric secretion of the fetus to the mother's blood pepsin levels cannot, of course, be excluded. That the blood pepsin peak is highest

one day post partum and falls only gradually suggests that if pepsin secretion is active in the fetus, it does not play a significant part.

This finding of a general increase in blood pepsin (or at the very least the failure to find a decrease in blood pepsin during pregnancy) seems to explain the previously accepted paradox of a high prevalence of heartburn in the presence of what has been accepted as achlorhydria during pregnancy. A hiatus hernia with reflux of gastric contents into the esophagus is apparently common during pregnancy. A decrease in acid secretion would not have been expected to lead to increased heartburn; the less acid the regurgitation into the esophagus, the less esophagitis and heartburn. Evidence has been presented here that during the period when heartburn is most prevalent, there is at least a normal gastric secretory response, and very probably an increased gastric secretion. The literature is in disagreement on this point, and our findings agree with those of Way[9] and of Clark and Tankel,[10] as opposed to the bulk of published reports.[11-14]

TABLE 4. *Blood Pepsin during Trimesters of Pregnancy.*

BLOOD PEPSIN UNITS								
1ST TRIMESTER	2D TRIMESTER		3D TRIMESTER		
233	393	410	418	280	400
400	260	260	330	290	368
234	285	435	348	338	345
272	200	298	443	412	393
325	316	288	355	350	270
333	278	330	265	580	120
295	350	273	308	340	350
	342	280	185	210	487
av. 299	414	315	275	325	294
No. 7	298	300	580	447	438
	389	243	260	224	402
	233	365	397	266	472
	237	185	383	438	225
	273	273	450	465	265
	263	220	260	295	410
	305	280	443	348	275
		385	265	518	304
			403	308	752
	av. 308		378	320	600
	No. 33		263	453	463
			375	238	307
			238	375	270
			378	365	250
			298	455	253
			333	368	340
			425	495	812
				330	620
					274
					224
				av. 361	
				No. 83	

The clinical observation that peptic ulcer has a decreased recurrence rate during pregnancy has been accepted as being real, and the explanation logically followed from the apparent demonstration of achlorhydria or lowered gastric acid. However, the problem of amelioration of ulcer is complicated by the fact that early in pregnancy the patient is well instructed in the importance of regular feeding and emphasis is placed upon adequate milk intake and general well-being. These are recommendations given to ulcer patients, and such treatment may lead to the misinterpretation of a favorable effect of pregnancy on the ulcer. Indeed, the frequency of ulcer in women of child-bearing age is difficult to ascertain, and until better data are available, there is no basis for stating that ulcer is significantly less frequent during pregnancy than in the female population as a whole.

SUMMARY AND CONCLUSIONS

The blood pepsin levels as an indirect index of gastric secretion were studied during pregnancy. The mean values in the first six months of pregnancy showed no significant variation from the normal. From the seventh month on, there was a rise in the levels that reached a peak on the day after delivery, subsequently falling to normal values by one hundred and twenty to one hundred and forty days post partum.

TABLE 5. *Average Blood Pepsin Values in Consecutive Months.*

TIME OF ASSAY	AVERAGE BLOOD PEPSIN LEVEL
	units
7th mo.	367
8th mo.	383
9th mo.	384
1 day post partum	456
42 days post partum	371
120-140 days post partum	331

The results presented showed no decrease in gastric secretion during the first two trimesters of pregnancy. The rise in blood pepsin during the last trimester of pregnancy suggests some increase in gastric secretion during this period. These observations cast doubt on the clinical observation that the symptoms of peptic ulcer are alleviated during the course of pregnancy.

REFERENCES

1. Taussig, F. J. Uterus and stomach: their anatomic, physiologic and pathologic relationship. *J.A.M.A.* **51**:1005-1009, 1908.
2. Adair, F. L., Ryerson, M. C., and Stieglitz, E. J. *Obstetric Medicine: The diagnosis and management of the commoner diseases in relation to pregnancy.* 743 pp. Philadelphia: Lea & Febiger, 1934.
3. Hurst, H. F., and Stewart, M. J. *Gastric and Duodenal Ulcer.* 544 pp. New York: Oxford, 1929. P. 153.
4. Mulsow, F. W., and Brown, W. E. Peptic ulcer complicating pregnancy. *Am. J. Obst. & Gynec.* **31**:1041-1043, 1936.
5. Blakely, S. B. Abdominal pain in pregnancy. *J.A.M.A.* **101**:970-975, 1933.
6. Mirsky, I. A., Futterman, P., Kaplan, S., and Broh-Kahn, R. H. Blood plasma pepsinogen. I. Source, properties, and assays of proteolytic activity of plasma at acid reactions. *J. Lab. & Clin. Med.* **40**:17-26, 1952.
7. Spiro, H. M., Ryan, A. E., and Jones, C. M. Utility of blood pepsin assay in clinical medicine. *New Eng. J. Med.* **253**:261-266, 1955.
8. *Idem.* Relation of blood pepsin to gastric secretion, with particular reference to anacidity and achylia. *Gastroenterology* **30**:563-582, 1956.
9. Way, S. Relation between gastric acidity and anterior-pituitary-like hormone content of urine in pregnant women. *Brit. M. J.* **2**:182-184, 1945.
10. Clark, D. H., and Tankel, H. I. Gastric acid and plasma histaminase during pregnancy. *Lancet* **2**:886, 1954.
11. Nakai, T. On gastric juice of pregnant women. *J. Biochem.* **5**: 465-477, 1925.
12. Arzt, F. Gastric juice during pregnancy. *Am. J. Obst. & Gynec.* **12**:879-883, 1926.
13. Mason, L. W. Gastric acidity in pregnancy. *Colorado Med.* **28**: 392, 1931.
14. Strauss, M. B., and Castle, W. B. Studies of anemia in pregnancy: gastric secretion in pregnancy and puerperium. *Am. J. M. Sc.* **184**:655-662, 1932.

SPECIAL ARTICLE

FACTORS IN STUDENT CHOICE OF GENERAL OR SPECIALTY PRACTICE*

MARY A. MONK, PH.D.,† AND MILTON TERRIS, M.D.‡

BUFFALO, NEW YORK

THE increasing trend toward specialization among medical graduates has been well documented by Weiskotten and Altenderfer.[1] Only 41 per cent of the graduates of American medical colleges in 1915 were found to be limiting their practice to a specialty a decade after graduation, as compared with 74 per cent of the graduates in 1945.[1,2] Recently, the Massachusetts Academy of General Practice conducted a survey of 830 students in the three medical schools in Boston and 158 interns and residents in hospitals in the State. Of the first-year medical students, 44 per cent intended to enter general practice, 48 per cent were undecided, and only 8 per cent had decided to become specialists. Fourth-year students presented a different picture: 25 per cent intended to enter general practice, 16 per cent were undecided, and 59 per cent planned to specialize. Eighty-one per cent of the interns and residents who replied planned to enter specialty practice.[3]

Similarly, a survey by the magazine *Medical Economics* in 1954 showed that 60 per cent of more than 1000 senior medical students intended to enter specialty practice.[4] The major reason given for this choice was the desire to practice "better medicine"; other representative comments included the following: a preference for "shorter hours" or "more orderly existence"; "specialization is less complicated"; "it's less routine"; and "the specialist has an easier time getting hospital privileges." Of particular interest is the fact that among the surveyed students, the most popular specialty was found to be internal medicine, with surgery, pediatrics, and psychiatry and neurology following in that order. The students intending to become general practitioners gave as the main reason for their choice the greater diversity of general practice. Other reasons were as follows: "The GP is closer to his patients"; "I can't afford to finance my way through a residency"; "I don't want to spend the rest of my life in training"; and "the place I intend to practice in is too small to support a specialist."

The present study is an attempt to determine some of the factors involved in student choice of general practice or specialty. Since 1951, fourth-year students at the University of Buffalo School of Medicine have indicated their preferences in the medical-school yearbook. For the classes 1951-55 these preferences have been correlated with data obtained from the medical-school record on each student's age, class standing, father's occupation and community of origin. In addition every member of the class of 1955 was interviewed to obtain his reasons for choice of general practice or specialty, and the interview findings were cross-checked with an anonymous questionnaire filled out by the same students.

Of the 327 senior students in the five classes 112, or 34 per cent, chose general practice, 173, or 53 per cent, chose a specialty, and 42, or 13 per cent, indicated no preference. The most popular specialties were internal medicine, 71; surgery, 33; obstetrics and gynecology, 23; psychiatry, 16; and pediatrics, 13. The proportion of fourth-year students choosing specialty practice, although somewhat lower than the 60 per cent reported in the *Medical Economics* survey and the 59 per cent reported for the Boston schools, supports the general finding of these studies that a majority of fourth-year medical students intend to specialize.

CLASS STANDING

Scholastic standing was found to be significantly related to preferences for different types of practice. Only 17 per cent of the senior students with high class standing intended to enter general practice, as compared with 48 per cent of those in the low scholastic group. Conversely, 73 per cent of the students with high class standing intended to specialize, as compared with only 38 per cent of those in the low scholastic group (Table 1). No differences were found in class standing among students choosing different specialties.

To determine the relation of class standing to specialization among graduates of an earlier generation, an additional study was carried out for the 299 physicians who graduated from the University of Buffalo School of Medicine during the five-year period from 1930 through 1934. Class standings were determined from medical-school records. Specialist status was obtained from the *American Medical Directory* for 1950, with the use of criteria described in a previous paper[5]; only those designated as limiting their practice to a specialty were included as specialists. The results are shown in Table 2.

As of 1950, 55 per cent of the graduates of 1930-34 were in general practice. This is in sharp contrast to the preferences of the 1951-55 graduates, only 34 per cent of whom indicated general practice as their

*From the departments of Postgraduate Education and Preventive Medicine and Public Health, University of Buffalo School of Medicine.

†Research associate in postgraduate education and associate in preventive medicine and public health, University of Buffalo School of Medicine; lecturer in psychology, University of Buffalo.

‡Assistant dean for postgraduate education and associate professor of preventive medicine and public health, University of Buffalo School of Medicine.

field of choice at time of graduation. Furthermore, whereas the 1951-55 graduates with high class standing showed a much greater preference for specialty practice than those with low scholastic achievement, the differences in class standing among the general practitioners and specialists who graduated in 1930-34 were not statistically significant.

TABLE 1. *Percentage of Fourth-Year Students Indicating Choice of General Practice or Specialty, by Class Standing.**

CLASS STANDING	TOTAL NO.	PREFERENCE			
		GENERAL PRACTICE	SPECIALTY	NONE	TOTALS
		%	%	%	%
High	111	17.1	73.0	9.9	100.0
Middle	118	39.0	46.6	14.4	100.0
Low	98	48.0	37.7	14.3	100.0
Totals	327	34.2	53.0	12.8	100.0

*Chi-square = 30.33; $P < 0.001$.

These data, of course, are not truly comparable, since the statistics on the 1951-55 graduates concern only preferences at the time of graduation, and for the 1930-34 graduates the data refer to the type of practice actually engaged in many years after graduation. A previous study has demonstrated that changes in type of practice continue to occur long after graduation,[5] and it is quite possible that by 1970 the proportion of general practitioners in the 1951-55 classes

TABLE 2. *Percentage of 1930-34 University of Buffalo School of Medicine Graduates Engaged in General or Specialty Practice in 1950, by Class Standing at the Time of Graduation.**

CLASS STANDING	TOTAL NO.	TYPE OF PRACTICE		
		GENERAL PRACTICE	SPECIALTY	TOTALS
		%	%	%
High	99	51.5	48.5	100.0
Middle	109	53.2	46.8	100.0
Low	91	61.5	38.5	100.0
Totals	299	55.2	44.8	100.0

*Chi-square = 2.19; $P > 0.3$.

will also show no relation to class standing. Nevertheless, there is a suggestion in these data of a shift in values during the past twenty-five years, with general practice emerging as a much less attractive alternative to students of high scholastic achievement.

AGE AT GRADUATION

Age at graduation is apparently an important factor in the choice of type of practice. Almost half the students twenty-eight years of age or older intended to enter general practice as compared with a little over a quarter of the younger students. (Table 3). There were no age differences among students choosing different specialties.

Age and class standing are not independent variables, however. Of the students twenty-eight years of age or older, only 17 per cent had high class standing, as compared with over 40 per cent of the younger students (Table 4).

To isolate the two variables of age and class standing, the relation of class standing to choice of type of practice was studied for each age group (Table 5).

TABLE 3. *Percentage of Fourth-Year Students Indicating Choice of General Practice or Specialty, by Age at Graduation.**

AGE AT GRADUATION	TOTAL NO.	PREFERENCE			
		GENERAL PRACTICE	SPECIALTY	NONE	TOTALS
yr.		%	%	%	%
25 or less	117	25.6	59.9	14.5	100.0
26-27	103	29.1	59.2	11.7	100.0
28 or more	107	48.6	39.2	12.2	100.0
Totals	327	34.2	53.0	12.8	100.0

*Chi-square = 15.85; $P < 0.01$.

For students twenty-five years of age or younger at time of graduation, only 10 per cent of those with high class standing intended to enter general practice as compared with 50 per cent of those in the low scholastic group. The comparable figures for the group from twenty-six to twenty-seven years of age were 14 and 50 per cent; for both age groups the over-all differences are significant. But for students twenty-eight years of age or older at time of graduation, the difference disappears; 45 per cent of those

TABLE 4. *Percentage of Fourth-Year Students in Each Class Standing, by Age at Graduation.**

AGE AT GRADUATON	TOTAL NO.	CLASS STANDING			
		HIGH	MIDDLE	LOW	TOTALS
yr.		%	%	%	%
25 or less	117	43.6	39.3	17.1	100.0
26-27	103	40.8	34.0	25.2	100.0
28 or more	107	16.8	34.6	48.6	100.0
Totals	327	33.9	36.1	30.0	100.0

*Chi-square = 31.65; $P < 0.001$.

with high class standing intended to enter general practice, as compared with 46 per cent of those in the low scholastic group. Age, apparently, is a powerful factor in choice of type of practice; regardless of class standing, about half of all students twenty-eight years of age or older at time of graduation intended to enter general practice.

FATHER'S OCCUPATION

Information on father's occupation was obtained from the application forms for admission to medical school, and the occupations were assigned to cate-

gories similar to those used by the Census Bureau. There is probably some error in these assignments, particularly in the "business owner and other white collar" group, since the information available was not always easy to interpret.

No significant differences were found in choice of general practice or specialty by students coming from different occupational segments of the population (Table 6). It is of interest that the preferences of physicians' sons were not significantly different from those of other students.

Community of Origin

The size of community from which the students originated was found to have no significant relation to choice of general practice or specialty (Table 7).

TABLE 5. *Percentage of Fourth-Year Students in Different Age Groups Indicating Choice of General Practice or Specialty, by Class Standing.*

Class Standing	Total No.	Preference			
		General Practice	Specialty	None	Totals
		%	%	%	%
25 yr. of age or under*:					
High	51	9.8	80.4	9.8	100.0
Middle	46	32.6	47.8	19.6	100.0
Low	20	50.0	35.0	15.0	100.0
Totals	117	25.6	59.9	14.5	100.0
26-27 yr. of age†:					
High	42	14.3	76.2	9.5	100.0
Middle	35	31.4	54.3	14.3	100.0
Low	26	50.0	38.5	11.5	100.0
Totals	103	29.1	59.2	11.7	100.0
28 yr. of age or over‡:					
High	18	44.5	44.5	11.0	100.0
Middle	37	54.1	37.8	8.1	100.0
Low	52	46.2	38.4	15.4	100.0
Totals	107	48.6	39.2	12.2	100.0

*Chi-square = 18.95; $P < 0.001$.
†Chi-square = 11.47; $P < 0.05$.
‡Chi-square = 1.54; $P > 0.80$.

Weiskotten and Altenderfer,[1] on the other hand, found a direct relation between size of community of prior residence and the percentage of 1935 and 1940 graduates engaged in specialty practice in 1950. It should be emphasized at this point that our study is concerned only with preferences at time of graduation, and that the findings for the same classes may be quite different in 1965.

Reasons Given for Preferences

To obtain some indication of the reasons for student choice of general or specialty practice, all the 70 students in the class of 1955 were interviewed by a senior medical student, who was given some training in interviewing technics. The students were told that their replies would remain anonymous, and were asked not to discuss the survey with their classmates. Each interview lasted approximately twenty minutes.

TABLE 6. *Percentage of Fourth-Year Students Indicating Choice of General Practice or Specialty, by Father's Occupation.**

Father's Occupation	Total No.	Preference			
		General Practice	Specialty	None	Totals
		%	%	%	%
Physician	42	38.1	54.8	7.1	100.0
Other professional	61	31.1	57.4	11.5	100.0
Business owner & other white collar	138	29.0	58.0	13.0	100.0
Skilled, semiskilled & unskilled worker	65	46.2	41.5	12.3	100.0
Unknown	21	33.3	38.1	28.6	100.0
Totals	327	34.2	53.0	12.8	100.0

*Chi-square = 12.73; $P > 0.10$.

Of the 70 students interviewed, 31 indicated a preference for general practice: 13 intended to do general practice only; 4 intended to do general practice with special attention to a specialty; and 14 were undecided but tended to prefer general practice.

The reasons given for preferring general practice fell into several categories:

The variety of general practice was mentioned 14 times in such statements as the following: "like to work with all types of cases"; "many interesting fields, hate to give them up for one specialty"; "like all phases of medicine"; and "general practice more of a challenge than a specialty."

Interest in being a family doctor and having good doctor-patient relations was mentioned 7 times in such statements as the following: "want to be a family doctor, get to know entire family"; "gratification of treating entire patient instead of one system"; "relation to patient more rewarding than as specialist"; and "know patients better as general practitioner."

Interest in small-town practice was mentioned 6 times in such statements as the following: "would like to practice in small community, which would require general practice"; and "feel that I will be happiest in small community, and there only general practitioner can give best service."

Desire to enter practice soon was mentioned 5 times in these statements: "easier to get started"; "age too old"; "have to go into Army"; "would not like to spend too many more years in training"; and "sick of academic situation."

Miscellaneous reasons were given 6 times in such statements as: "need for general practitioners";

"like idea of being community doctor"; and "father a general practitioner."

Of the 39 students who did not indicate a preference for general practice 29 preferred a specialty, 8 were undecided but tended to prefer a specialty, and 2 were completely undecided. Of the 37 preferring a specialty 17 intended to enter internal medicine, 7 surgery, 4 obstetrics and gynecology, 2 psychiatry, 2 anesthesia, 1 pediatrics, 1 public health, and 1 ophthalmology, and 2 had no preferences. Various reasons were given for interest in a specific field, such as the following: "broad field — next best to general practice" and "represents real medicine" (internal medicine); "like to work with hands — definitive results" (surgery); "interested in this field before medical school" (psychiatry, ophthalmology); "young, growing field" (anesthesia); and "stimulating field, chance to do something good for the community in general on a major scale" (public health).

TABLE 7. *Percentage of Fourth-Year Students Indicating Choice of General Practice or Specialty, by Size of Community of Origin.**

SIZE OF COMMUNITY†	TOTAL NO.	PREFERENCE			
		GENERAL PRACTICE	SPECIALTY	NONE	TOTALS
		%	%	%	%
500,000 or more	204	30.9	58.8	10.3	100.0
10,000-499,999	86	40.7	40.7	18.6	100.0
9,999 or less	37	37.8	48.7	13.5	100.0
Totals	327	34.2	53.0	12.8	100.0

*Chi-square = 9.13; $P > 0.05$.
†Size based on 1950 population; size used for suburbs that of metropolitan area in which suburb located.

The reasons given for preferring specialty to general practice fell into these categories:

The inability to cover all fields of medicine well, mentioned 26 times in such statements as the following: "can do more for people by knowing a lot about one subject"; "don't learn enough in medical school and internship to go into practice"; "it is impossible to master all fields"; "specialty allows one to do better work"; "went with general practitioner for a month — do not think he can cover field of medicine"; and "field of medicine so broad would feel inadequate and afraid to go into general practice."

Deficiencies in status and privileges of general practitioners, mentioned 16 times, as in the following replies: "in my home town general practitioners are held back in medicine and surgery"; "general practitioners are abused too much"; "I do not like to hear, 'Oh, he's a GP,' with all its connotations"; "my father was a general practitioner, and I had firsthand appreciation of life of general practitioner with its restrictions, night calls and so forth"; and "general practitioners have a tough time in hospitals."

Better conditions of work and higher incomes of specialists, mentioned 11 times, in such statements as the following: "financial return"; "regular hours"; "more leisure time for study and so forth"; and "more time to spend with family."

To provide a check on the interview study and to furnish quantitative data on the relative importance of the various reasons given, the entire class was asked several months after completion of the interviews to fill out an anonymous questionnaire according to these instructions: "the following are some reasons given in the recent interview study of the senior class as to why general practice or a specialty was preferred; for both general practice and specialty indicate what you think was the relative importance of the different reasons in determining the choices made by the seniors."

TABLE 8. *Importance of Reasons Indicated for Seniors' Choice of General Practice.*

REASON	MUCH IMPORTANCE	SOME IMPORTANCE	LITTLE IMPORTANCE	NO IMPORTANCE
	NO. OF REPLIES	NO. OF REPLIES	NO. OF REPLIES	NO. OF REPLIES
Like variety of work in general practice	20	7	—	—
Can treat patient as whole in his family unit	19	6	2	—
Better doctor-patient relation in general practice	17	8	1	1
Want to practice in small community	11	10	6	—
Can start sooner & begin earning living sooner than in specialty	9	7	8	3
There is need for general practitioners	3	17	5	2
No particular interest in any specialty	1	7	9	9
Do not want to continue in academic situation	1	4	11	11
Specialties overcrowded	0	3	12	12
Have to go into Army	0	3	8	16
Emphasis in medical school has been on training general practitioners	0	1	9	17

The students preferring general practice rated the reasons for the seniors' choice of this type of practice in the order of importance shown in Table 8.

The students preferring to specialize rated the reasons for the seniors' choice of specialty practice as indicated in Table 9.

The results obtained by questionnaire are quite comparable with those obtained in the interview study. It should be recognized, however, that only 70 students from a single class provided the data for this aspect of the study. It should also be noted that when the students preferring specialties were asked

to rate the reasons for their colleagues' choice of general practice, they tended to place more importance on the need to begin earning a living sooner. Conversely, students choosing general practice gave considerably more emphasis to regular hours and more leisure time as a reason for their classmates' choice of a specialty. It is possible, therefore, that under the conditions of the interview and questionnaire methods used, the students tended to mention and emphasize the more socially acceptable reasons for their choice.

Discussion

The results obtained in this study provide additional information on the trend toward specialization of medical graduates. Only 112, or 34 per cent, of the 327 fourth-year students preferred general practice.

TABLE 9. *Importance of Reasons Indicated for Seniors' Choice of Specialty Practice.*

Reason	Much Importance	Some Importance	Little Importance	No Importance
	No. of replies	No. of replies	No. of replies	No. of replies
Can be more confident knowing 1 field well	22	8	6	1
1 yr. of internship not enough for practicing medicine	18	11	8	1
Can help patients more by knowing 1 field well than by trying to cover all medicine	15	16	3	3
Have always been interested in particular specialty	12	14	10	2
Can keep up with literature & attend professional meetings as specialist	8	16	10	4
Status of general practitioner poor & not likely to get any better	8	13	10	6
Want to do teaching & research, which require specialty status	8	11	10	9
Emphasis on medical training has been on specialization	7	16	8	6
Difficult to get hospital appointment as general practitioner	6	17	11	4
Regular hours & more leisure time than in general practice	5	15	12	6
Better income than in general practice	4	12	11	10

Furthermore, these tended to be students with low scholastic achievement and those in the older age group regardless of class standing. It is clear that the younger and more successful students regard general practice as a much less attractive alternative.

This trend toward specialization has aroused a good deal of concern. For example, Dr. Philip F. Fortin, president of the Massachusetts Academy of General Practice, concluded from the Boston survey of medical students and house-staff members that "unless constructive conservation measures are taken immediately, the general practitioner — the family doctor so essential to the treatment of the whole patient — may become obsolete."[3] Similarly, the *New England Journal of Medicine* commented editorially as follows:

> The fundamental role of the family medical adviser in providing the basic medical needs of a family and community has long been recognized and emphasized. If, however, the general practitioner is in danger of becoming obsolete — in other words, if his role is diminishing to that of a supernumerary or "walk-on" — perhaps the time has come for more than lip service.[4]

Closer examination of the data of the present study indicates, however, that a somewhat different interpretation may be considered. It is true that only 112 of the 327 senior students chose general practice. But of the 173 students choosing a specialty, 71 intended to practice internal medicine, which was by far the most popular of the specialties chosen. If the internist is considered to belong in the category of "general physician," the total number of students choosing to become generalists was 183, or 56 per cent of the 327 students studied. The previous minority of 34 per cent general physicians is thus converted into a majority intending to practice general medicine.

The propriety of including physicians in general practice and internal medicine in a single category of "general physicians" may be questioned. On the other hand, it should be noted that Dr. Fortin equates the "general practitioner" and the "family doctor," whereas the editorial in the *New England Journal of Medicine* similarly treats the "family medical adviser" and the "general practitioner" as one and the same person despite the fact that this no longer reflects the actual situation for many families. Particularly in urban areas, there is an ever-increasing tendency for the general practitioner to be replaced in his role as family physician by a general physician for adult members of the family, the internist, and a general physician for children, the pediatrician.

It is true that the physician in general practice is much more of a generalist than the physician who limits his practice to internal medicine. Hospital restrictions, however, are increasingly limiting the amount of surgery performed by general practitioners, and the growth of specialty practice in obstetrics, pediatrics and other fields, particularly in urban areas, is having a similar though perhaps less marked effect. The result is that for a growing number of general practitioners the content of practice is mainly in the field of internal medicine.

With these trends in mind, an alternative interpretation of the data on student preferences is possible — namely, that the majority of fourth-year medical students intend to become general physicians. In the future such general or family physicians will tend to be more limited in scope of practice and more highly trained than the classic general practitioner.

The changing character of the general physician

is a necessary response to the enormous expansion of medical knowledge and technic in the past fifty years. This is reflected in the statements made by the students themselves. When asked to rate the various reasons given for choice of specialty practice, they considered the following items to have the greatest importance: "can be more confident knowing one field well"; "one year of internship not enough for practicing medicine"; and "can help patients more by knowing one field well than by trying to cover all of medicine."

Summary

This study of the 1951-55 senior classes of the University of Buffalo School of Medicine demonstrates that a majority of the students at that school intend to specialize and only a third prefer general practice. The preference for general practice is greatest among students of low scholastic achievement and older students regardless of class standing; there is no significant relation to father's occupation or size of community of origin. Although the data are not truly comparable, it is of interest that study of the 1930-34 classes shows no significant relation between class standing and subsequent specialization.

An interview study of the 1955 senior class indicates that the major reasons given for preferring general practice are the variety of work, interest in being a family doctor and having good doctor-patient relation, interest in small-town practice and desire to enter practice soon. The major reasons given for choosing specialty practice are the inability to cover all fields of medicine well, interest in a particular specialty, deficiencies in status and privileges of general practitioners and better conditions of work and higher incomes of specialists.

More than half the 327 students in the study indicated a preference for either general practice or internal medicine. The interpretation is offered that a majority of students still intend to become general physicians, and that the general or family physician of the future will be more limited in scope of practice and more highly trained than the traditional general practitioner. It is suggested that current trends represent not the destruction of the general physician but his transformation.

We are indebted to Dr. James R. Nunn for assistance in the interview study.

References

1. Weiskotten, H. G., and Altenderfer, M. E. Trends in medical practice: analysis of distribution and characteristics of medical college graduates, 1915-40. *J. M. Educ.* **27**:3-41, 1952.
2. Weiskotten, H. G. Trends in specialization. *J.A.M.A.* **160**:1303-1305, 1956.
3. Editorial. Vanishing American. *New Eng. J. Med.* **251**:283, 1954.
4. Croatman, W. Tomorrow's doctor: what are his goals? *M. Economics* **31**:124-130, 1954.
5. Terris, M., and Monk, M. Changes in physicians' careers: relation of time after graduation to specialization. *J.A.M.A.* **160**:653-655, 1956.

MEDICAL PROGRESS

HUMAN INFERTILITY

Fred A. Simmons, M.D.*

BOSTON

INFORMATION from reliable sources indicates that for every 85 couples producing one or more living offspring, there are still 15 couples in this progressive country who do not conceive. Therefore, modern medicine must concern itself with the challenge of what can be done for more than 3,000,000 involuntarily childless married couples in the United States. Indeed, this is a world-wide problem. Since the founding of the American Society for the Study of Sterility, only thirteen years ago, groups of physicians, specialists, psychiatrists and veterinarians interested in promoting human reproduction have been formed all over the globe. At least three journals, with a combined circulation of over 4000, devoted to fertility and sterility problems have sprung into being. In order of seniority these are the *Journal of Fertility and Sterility* (1950), official organ of the American group; the Mexican *Journal of Sterility* (1950); and *Fertility* (1955), official organ of the International Fertility Association.

*Instructor in gynecology, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

Some Causes of Sterility

Regarding the chief causes of sterility a good deal depends upon the part of the world one inhabits. In Paris, for example, there is noted preponderance of closed fallopian tubes, whereas in Israel there is a higher incidence of tuberculosis of the genitalia. Throughout the literature, the usual causes run approximately as follows: tubal factor, 33 per cent; cervical factor, 40 per cent; male factor, 30-50 per cent; and hormonal factor, 15 per cent.

Before embarking upon the correction of these factors one must review the minimal diagnostic maneuvers available in 1956. These, for the sake of brevity, are listed in tabular form, for recourse to any of several recent well conceived textbooks on human fertility enumerates not only the indication for such tests but also their execution. Suffice it to say here that several avenues of investigation are dependent upon a surgical training, or at least a postgraduate course of instruction not only in the principles of sterility study but also in actual performance of such

tests. Each year deaths from injudicious insufflation of the tubes are reported. Perforation of the uterus occurs even in trained hands. The interpretation of tubal tests by gas, kymography or x-ray study is often wrong even in skilled hands. The omission of any of these minimal diagnostic procedures may result in failure instead of success.

It does not behoove the physician, the family doctor, obstetrician, gynecologist or psychiatrist to assume that "this patient must be all right — I brought her into the world" or that another "is unable to conceive because she has a tipped womb" (this is rarely a factor, but can be an important one). Another mistaken idea is represented by the statement, "this patient has a little irregularity of the menses, but hormones will fix her up." In Chicago, in June, 1956, at the annual meeting of the American Society for the Study of Sterility, Dr. Carl Heller, of Oregon, stated: "There is very little benefit from hormone therapy in infertility."* It is often equally fallacious to explain infertility on the grounds that a patient "has a mother complex and really does not want a child"; perhaps she does not, but often her husband has no spermatozoa at all, or too few.

TABLE 1. *Routine Minimal Diagnostic Procedures for the Wife.**

History & physical examination
General laboratory examinations:
Blood Wassermann test
Complete blood count, including sedimentation rate if white-cell count is high
Urinalysis
Basal metabolism
Tubal insufflation
Endometrial biopsy
Miscellaneous diagnostic tests:
Intracervical postcoital examination
Incompatibility test with cervical mucus & semen
Cervical smear; gram stain.
Vaginal hanging-drop & stained smear
Ovulation timing:
Endometrial biopsy
Basal body temperature

*Based on Simmons, F. A. Diagnosis and treatment of infertile couple. *South. M. J.* **46**:33-39, 1953.

One of the frustrating items in this specialty of sterility study is the indifference of many physicians confronted by a couple whose chief complaint is failure to reproduce. Even more distressing is the plight of the couple suffering from habitual abortion. Too often the wife takes all the blame when the husband may have been radiated or exposed to heavy-metal poisoning, or may suffer from chronic intoxication from alcohol, nicotine, diabetes or other noxious influences.

*M. Edward Davis, professor of gynecology and obstetrics and head of the Department of Gynecology and Obstetrics, University of Chicago School of Medicine, and editor of *Fertility and Sterility*, concurs with this statement, as does W. W. Williams, of Springfield, Massachusetts, founder and first president of the American Society for the Study of Sterility and author of *Sterility: The diagnostic survey of the sterile couple* (1953).

Tables 1 and 2 show the minimal diagnostic steps in the study of barren wives and husbands.

It should be obvious that any test will be followed by a few conceptions. Sharman, of Scotland, showed that passing a uterine sound through the cervix to the fundus of the uterus was followed by pregnancy in 17.8 per cent of cases. Weir and Weir state that 26 per cent of the infertile couples conceive without any treatment. A delay of six weeks from the date

TABLE 2. *Routine Minimal Diagnostic Procedures for the Husband.**

History & physical examination
General laboratory examination:
Blood Wassermann test
Complete blood count, together with sedimentation rate if white-cell count is high
Urinalysis
Prostatic secretion, fluid specimen & stained smear
Basal metabolism
Semen examination:
Volume
Motility
Number of spermatozoa per cubic millimeter
Type & ratio of abnormal spermatozoa

*Based on Simmons, F. A. Diagnosis and treatment of infertile couple. *South. M. J.* **46**:33-39, 1953.

the couple decide to consult a physician (preferably a qualified fertility specialist) and the time of the first appointment may allow conception to occur. There must be something to the idea of a "psychologic block."

Perhaps the best proof that a given test will be followed by prompt conception is the case of 1-child (or 2-child, 3-child or 4-child) sterility. There are hundreds of well documented cases in which conception occurred in the same cycle in which the tubes were insufflated successfully or within four cycles thereafter. Certain clinics prefer the introduction of radiopaque material to carbon dioxide for this purpose.

With this preliminary reference to the need for an interested physician, equipped with adequate time, skill, sympathy and diagnostic tools, and laboratory facilities, one should consider what therapy has to offer.

TUBAL FACTOR

The most important single contribution to promoting fertility — besides regular, completed coitus — is still the ingenious discovery by Rubin (April 10, 1920) of uterotubal insufflation. Despite elaborate apparatus, kymographic drums, pressure gauges and cannulae, the basic principle consists in determining if carbon dioxide gas (not air) will traverse the delicate, small, tortuous lumen of the salpinx. Whereas Rubin originally found it necessary to prove such passage by x-ray demonstration of gas under the diaphragm he soon recognized unilateral or bilateral shoulder pain as a *sine qua non* of successful trans-

tubal passage of the gas when the patient sat up or stood. It is a sad commentary today that many physicians diagnose tubal patency or nonpatency only by the introduction of an opaque fluid made visible on x-ray study or by a similar introduction of gas under pressure and then base the diagnosis on what they see or hear or what the manometer reads. It is still essential, even in 1956, for the patient to report shoulder pain on sitting or standing. In a similar vein it is almost absurd to warn that the patency of the tubing and cannula must be observed before the test lest the obstruction be in the apparatus and not in the patient. One unsuccessful test does not mean damaged tubes. Two or more satisfactorily executed insufflations are indicated before obstruction is predicated.

Campos da Paz was among the first to point out that uterotubography (hysterosalpingography) and uterotubal insufflation complemented one another. From his work it should be obvious that although certain tubes allow the gas to pass, they may not be normally patent and in a few months the patient should be offered tubography. Palmer believes that 63 per cent of his patients conceive after tubography routinely done whereas before he used this maneuver in every case 21 per cent conceived after gaseous insufflation.

It must be mentioned again and again that the use of room air or oxygen is a likely source of fatal air embolism.

Clinics depending entirely on x-ray visualization are misled by the vagaries of the tubes into a false opinion about patency. McLane condemns inadequate work-up as a factor in 24 of 283 cases that his clinics investigated and states, "Tubal insufflation and hysterosalpingograms continue to be the *outstanding therapeutic measures* in the *treatment* of infertility [italics mine]." The tubogram should also be followed in a few months by a carefully performed gaseous insufflation. Certainly, all diagnostic skills must be utilized before tubal surgery, for the salvage with surgery is less than 20 per cent, as pointed out by Greenhill in 1939 and 1956.

Recent advances include the introduction of various opaque mediums for salpingography. Although Lipiodol and Iodochlorol have stood the test of time, economy and safety, some enthusiastic investigators have urged the use of Ethiodol, Salpix and Visco-Rayopaque.

There is said to be a hazard in instilling an oily medium into the tubes. This may be true only in already damaged tubes. Supporters for the water-soluble mediums (Rock et al.) consider them less noxious, but those in favor of the oily mediums depreciate the more fluid materials as being too transiently visible, absorbed too quickly and devoid of the so-called stretching quality of the more viscous oils. Furthermore, proper use of the established oils is rarely attended by pain whereas the newer substances are more painful according to patients who have had both tests. Incidentally, almost all authorities agree that neither uterotubal gas nor liquid tests should be performed with the patient under anesthesia, for the danger of perforation or hemorrhage or a flare-up of an unsuspected salpingitis is increased. Sharman, of Scotland, and Grant, of Australia, both men with years of experience and many tests, report that gas may be used at pressures up to 300 mg. of mercury without harm, but for the neophyte and almost all the rest, it is adequate and safer to limit the pressure to 200 mg. and to stop before attaining that level if the patient complains of undue or unexplained pain. Finally, a word must be said about the hazard of introducing a foreign body (oil or aqueous) against the delicate epithelium and cilia of these susceptible tubes since, in inexpert hands, tubal blockage may be precipitated by this diagnostic test.

Grant, especially, and Sharman have advocated repeated tubal insufflation coupled with pelvic heat and sexual rest as a method superior to tubal surgery in making damaged tubes function. Grant reports 18 per cent of pregnancies after repetitive gas treatment against 22.2 per cent after surgery. It is true that blocked tubes can be made patent by time alone, sexual rest, short-wave diathermy and antispasmodics. In 1956 Finegold reported cortisone to be useful in opening such tubes, but only one series has been discovered in the literature, in which 23 patients conceived from 100 cases selected because of no ascribable cause of infertility.

Tubal Surgery

As for tubal surgery, the most important current teaching is that since the results in the best hands are poor (Rock, 24 per cent, Greenhill, 6.6 per cent, and Siegler and Hellman, 22.6 per cent) surgical attack should be limited to those in teaching clinics or with considerable experience. Of course, any surgeon may have one success with one case or may be even more lucky, but there are not enough suitable cases to permit the generalist who does abdominal surgery, the obstetrician who may see many normal tubes at cesarean section or for ligation, or even the busy general surgeon to encounter more than 3 or 4 candidates for such surgery each year. In the special clinics the trial-and-error method is still rampant. Polyethylene tubing seemed to offer hope (as suggested by Hellman, Rock, Castillo and Rutherford), but even that is losing favor, for the results are not superior enough, according to Rock, Greenhill and Sturgis, and there are hazards such as intestinal obstruction, loss of the tubing, salpingitis and plastic exudate around the fimbriae. In substance meticulous care in a few selected cases will produce success in only 22 per cent of the cases in the best surgeon's hands. This does not mean that the couple should

not be offered surgery. If the male is normal, spermatozoa live in the cervix, ovulation occurs regularly and the couple are told frankly that there is less than 1 chance in 4 that tuboplasty will permit a successful full-term pregnancy, they should be permitted to take the chance. Many physicians deny their patients that choice because the reported figures of success are so low.

One of the best contributions of the American Society for the Study of Sterility is the series of surveys instituted in its official organ, *Fertility and Sterility*, covering the ovary, the testis, the clinical use of testosterone, evaluation of testicular biopsy and, most recently, tubal plastic surgery. Here, Siegler and Hellman analyze a 15 per cent response from 4910 questionnaires sent to surgeons doing tuboplasty.

Only 11 per cent of the 734 surgeons replying had done more than 10 such operations. Only these figures were analyzed. There were no operative deaths. After the operative correction of occluded fallopian tubes (in skilled hands) there were 514 (22.6 per cent) pregnancies. Of these, 378 (73.5 per cent) were live births, 15.4 per cent ended in abortion, 9.1 per cent were extrauterine pregnancies, and 2.0 per cent ended in stillbirths.

Thus, although those who know most about the surgical attack on closed tubes repeatedly plea for the surgery to be referred to skilled men, even the expert fails to achieve the 25 per cent salvage pleaded for twenty years ago by Greenhill.

Mazer and Israel are even more stringent than most in their criteria of indications for surgery on the diseased fallopian tubes:

> It appears to be quite evident that a plastic operation on the Fallopian tubes is generally not justifiable unless there is a more specific indication for laparotomy, such as ovarian cyst or chronic appendicitis. If surgical treatment of occluded Fallopian tubes is undertaken specifically for the relief of sterility, the following exacting prerequisites should be met:
>
> 1. Absence of all other etiologic factors in the sterile union, irrespective of their unimportance.
> 2. Failure to open the Fallopian tubes by at least 10 transuterine insufflations at a pressure of 200 m.m. of mercury.
> 3. Demonstration by uterosalpingography that the occlusion is bilateral, that it is total, and that it is located at the fimbriated extremity in at least one tube.
> 4. Acceptance by the barren couple of a 5 percent chance of pregnancy as a result of the operation.

These rigid criteria are valid but a little too stringent since the patient and her husband may well continue to elect surgery and there is always the patient in a "hopeless case" who has children.

There is increasing evidence of ectopic pregnancy since the advent of antibiotic therapy for pelvic inflammatory disease, specific or not. Apparently, the drugs check the disease before total obstruction, but the salpinx is damaged and the fertilized ovum trapped before it can reach the uterus. Therefore, in patients who have a specific history of pelvic inflammation all tests to demonstrate normality of the tubes should be done *before* pregnancy is started. Until very recently there were no reported cases of successful pregnancy in women with tuberculous tubes. The disease is still very serious. Yet, from Israel (Rabau) come reports of open tubes and of a pregnancy that followed acute acid-fast salpingitis, and R. W. Dwight reports a successful pregnancy.

One cannot dismiss the subject of tubal closure without warning all that it is still possible with unprotected coitus with a diseased partner to contract venereal disease, which often causes blighted tubal function. Perhaps the greatest advance in the conquest of the damaged tubes will be when schools and parents wipe away the web of silence and ostracism about sex education. If a young adult or adolescent only knew that a few minutes of pleasure unprotected might result in permanent blockage of the male or female accessory sexual apparatus there would not be so many vasa deferentia or fallopian tubes diseased today.

Cervical Factor

Postcoital Test

In the last two years there have been over 30 papers discussing the factor of the cervix in infertile matings. There are still an appalling number of physicians who do not bother to do a postcoital test of the cervical mucus. This may be because their busy practice does not give them time to read or perhaps preconceived notions or prejudices make them consider it unnecessary. It is the *most necessary* test next to tubal insufflation and semen analysis. If positive the test indicates that the husband has spermatozoa, that the spermatozoa are alive, that they are reaching the cervix in adequate number, that the cervix is receptive to them and that there are no errors in coital technic. If the test is negative or poor there may be no spermatozoa, there may be errors in coital technic, the spermatozoa may be dead, the cervix may be hostile to the spermatozoa, and the couple will not conceive unless the spermatozoa get there alive.

In 1956 I have studied 6 men with adequate semen analysis, normal wives, what they thought was adequate, frequent coitus, but failure to ejaculate during coitus.

Recent advances include the scholarly paper of Swyer in the *British Studies on Fertility* (1955), which emphasizes certain points. Anyone interested in this phase should read Swyer's analysis of the results of 638 tests: "The finding of at least one test which is acceptable in respect to both sperm invasion and sperm activity within the mucus gives the patient a definitely better prognosis for conception, provided there be no major female infertility factors." In 638 tests carried out on 140 patients who conceived and 254 patients who have so far failed to conceive, he analyzed the mucus quality, invasion and

activity of the spermatozoa within the mucus correlated with the density and activity of spermatozoa in the husband's semen and presents well documented data: there was no difference in the mucus quality in the patients who did and did not conceive; the period of abstinence preceding coitus with the purpose of postcoital test had no influence on the result obtained, nor did the time elapsing between coitus and the test; furthermore the test was strongly influenced by the stage of the cycle at which it was performed, the eleventh to fourteenth days being best (I assume on the basis of a twenty-eight-day cycle); when the seminal fluid was acceptable, the chances of obtaining a positive test were far better, provided the mucus was acceptable, than when it was not, which suggests that in patients who do not conceive, mechanically inadequate coitus may be frequent; and, finally, a postcoital test should always be performed before one reaches a decision about the husband in the presence of faulty seminal analysis. Swyer concludes that the postcoital test has both prognostic and diagnostic value and fully *deserves its place among the standard procedures for the investigation of infertility.* Anyone capable of doing these tests must read this article in its entirety, together with the references to Bishop, Clift, Donald and Rubinstein et al. It is encouraging to realize that statistics are finally being applied to this most valuable clinical appraisal of the infertile couple. Since the majority of workers in the field of infertility are repeatedly emphasizing the importance of the postcoital test, the responsibility for not performing it rests with the physician who considers it unnecessary.

Fern Test (Palm Arborization Test)

Introduced by Rydberg, of Denmark, in 1948, popularized by Campos da Paz in 1953 and elaborated upon by Roland in 1953, this procedure, in brief, is based on the fact that dried cervical mucus forms fernlike fronds of dried sodium chloride from the eighth to the eighteenth day of the menstrual cycle more or less, indicating good estrin effect on the cervical mucus. In fertility work it is more useful when deficient, for it warns one of estrin lack. It may be used as a test for pregnancy. If the test is "Tipico" after the twenty-eighth day in the presence of amenorrhea, the woman is not pregnant.

Spinbarkeit (Spinability)

Spinbarkeit is a term introduced in 1945 by Clift to describe the capacity of semiliquids of going into threads. He discovered that the Spinbarkeit was higher at the time of ovulation and offered it as a means of pinpointing ovulation. Cohen et al. and Speck and Halter have offered office experience pointing out that it does in fact improve the opportunity of selecting the time of ovulation, but the former paper covers only 18 and the latter only 38 cases. The test requires daily office visits, which are impractical to most busy housewives and mothers, and it can well be omitted from routine studies, except in an investigative laboratory or office.

Vaginal and Cervical Smears

Many authors have written on the possibility of determining the optimum time of ovulation by study of the vaginal smears in addition to tests used in the study of the cervix. In fact one author suggests doing smears of the cervical cells. Reviews of the value of vaginal smears such as those introduced by Papanicolaou for determining the presence or absence of abnormal cells in the secretion of the female genital tract are highly useful in screening patients who may or may not have cancer. The Grahams, Fremont-Smith and others cannot confirm that the day of ovulation can be depicted from vaginal smears even today. This maneuver requires an extensive laboratory setup and a trained cytologist for proper interpretation and has as yet no useful application, except as a research tool, in the routine office of the physician investigating infertility.

Stenosis of the Cervix

A small, elongated cervix with a pinpoint os may be found to exhibit stenosis or narrowing of the cervical canal. This may occur at the external os and is reported at the internal os. In patients in whom everything else is normal, hospital admission for gentle but thorough dilatation followed by repeated office dilatation will sometimes relieve this condition in as high as 40 per cent of patients suffering from this defect, unless it is a disorder of hypoplasia of the entire genital apparatus. Even this may respond to large doses of estrogen periodically.

Surgery of the Cervix

Whereas in the first half of this century multiple surgical attacks were made on disorders of the cervix, these are rapidly becoming less popular throughout the world. There may be one exception to this when, after habitual abortion, it is demonstrated that the cervical function is altered by trauma or tears of the cervical pathway. This is a very rare finding, but R. Palmer and also Lash have suggested that a reefing operation of the cervix may relieve this condition. One should hesitate, however, to embark on such a procedure until all other causes of habitual abortion have been ruled out, including thorough investigation of the semen specimen of the husband and the husband himself.

Estrogen Stimulation

In faulty cervical insemination the most effective hormonal treatment still seems to be the technic in-

troduced by Hilda Lloyd, of England, in 1947. Shotton found that 0.1 to 0.25 mg. of stilbestrol for fourteen days improved cervical insemination in 87 per cent of 102 cases as compared to only 20 per cent after cautery.

Israel, Buxton, McLane, Simmons and others have found improved cervical penetrability and sperm motility after stilbestrol, as mentioned above, or often with penicillin or another antibiotic. In 1952 Buxton reported 21 successful cases in 95 stubborn cervixes after cervical culture and the appropriate drug for whatever organism. He was not able to confirm this in a subsequent study.

I agree with McLane "that dilating a cervical stenosis, overcoming tortuosity of the canal, or eliminating the sharp angulation of the cervix will often improve ovulation and the quality of the cervical mucus."

About 40 per cent of patients selected for dilatation and curettage and light cauterization followed by two or three dilatations in the office at ten-day intervals will conceive if the postcoital test was poor to unsatisfactory before this treatment. Conization has an extremely limited application if indeed it is not entirely passé.

McLane further states:

> When we eliminate specific vaginal and cervical infections which have to be treated according to the cause, the mucus may be abnormal because of: 1. a low grade nonspecific endocervicitis; 2. endocrine imbalance; 3. cervical stenosis; or 4. tortuosity or acute angulation of the cervical canal. This abnormal mucus is scant, tenacious, cloudy and when a post-coital test is attempted, it is almost impossible to remove the mucus from the cervical canal. Under the microscope the secretions are very cellular and show no evidence of sperm migration. We are convinced that the treatment of this condition should be conservative. Electrocoagulation and conization of the endocervix are still done too freely.

The Male Factor

It is comforting to read in the last half decade of the desirability of studying the infertile couple, not *just* the female. This implies that physicians, even gynecologists, and the lay public are beginning to accept the repeated maxim that was initiated about half a century ago by W. G. Haggart: "The woman should not bear the reproach until a microscopic examination of the partner has been made to determine the absence or presence of living healthy spermatozoa."

Willis Brown, reviewing *Sterility Investigations,* notes that the recent literature suggests that infertility is a syndrome of dual responsibility requiring complete and critical appraisal and analysis of both husband and wife. "The etiologies of infertility are multiple, and complete study of both husband and wife is essential."

In a treatise on the diagnosis and treatment of the infertile male in 1951, published in *Nelson's Surgery,* the author states:

> At the risk of offending some and antagonizing others it must be emphatically proclaimed that the family doctor and many eminent specialists need to admit their inadequacies in infertility study, and to acquaint themselves with the proper places to send these patients where trained personnel can reward the couple's somewhat substantial financial outlay with at least the 25 to 40 percent chance of successful pregnancy, on which even the best of clinics do not seem to improve year by year.

Likewise, it does not suffice for a casually produced semen specimen, poorly preserved, to be sporadically examined by a "technician" or family doctor or in fact anyone not trained in this procedure and to have its donor labeled normal or abnormal without being studied himself. In extreme cases the semen may not be that of the reputed husband.

Treatment is touched upon lightly or neglected by most articles on human sterility — or worse, on the basis of far too few cases, an enthusiastic author endorses a hormone, diet, or vitamin, or increased sexual activity or enforced abstinence as resulting in dramatic relief of the couple's barren state.

In June, 1956, in a Medical Progress report in the *Journal* entitled "Some Abuses of Drugs in Therapy," Dale G. Friend and George A. McLemore, Jr., state:

> It is essential that the physician . . . maintain a critical attitude concerning all preparations until they have demonstrated their merit by satisfying the rigid demands of critical investigators, careful observers and, perhaps as important as the former, the test of numbers and time . . .
>
> Unfortunately, these factors [undesirable effects and toxicity] combined with confusing terminology and complicated dosage patterns have made it nearly impossible for the average physician to understand completely and to employ wisely some of the more useful preparations. Consequently, certain abuses have developed that not only are undermining confidence in drug therapy but also can be harmful to the patient. . . .

For four years the so-called testosterone rebound phenomenon has plagued the public, culminating in a glowing article in a recent lay monthly reputedly "curing 80-90 percent of sterile husbands." In fact, a review of 64 clinicians who have used this therapy reveal that in carefully chosen cases it may be of help in 4 per cent. This program consists of large doses of testosterone propionate intramuscularly three times a week for six to ten weeks, which depresses spermatogenesis to zero. Then, for unexplained reasons, the spermatozoa level dramatically rebounds to higher than the original counts. The only trouble is that it does not do so very often, or it is elevated only cursorily and it *may never come back* to the pretreatment level (according to MacLeod). This type of therapy is dangerous except in selected cases in certain professional hands and is still experimental.

Varicocele

From Great Britain has come an awakening of interest in the effect of large varicoceles on male fertility. Van de Velde referred to this etiologic factor in the late 1920's, and Macomber always considered it a factor. Six years ago I reported pregnancy in 5 of 7 cases in which the husband was operated on. Now,

from Scotland and England, Tulloch and Handley describe increasingly good results from varicocelectomy. Carl Moore, whose recent death removed an expert in reproductive investigation, long ago demonstrated that heat was deleterious to spermatogenesis. Hotchkiss and MacLeod showed markedly reduced cell counts in 6 healthy volunteers subjected to artificially induced fever forty-two days after treatment. Recovery took over two months. More recently MacLeod reported marked oligospermia after chicken pox in an adult. It is not known whether the marked reduction in sperm was a result of the virus or the hyperpyrexia that it caused. At any rate, a large varicocele raises scrotal heat and influences both testes. To offset the weight and drag and discomfort of such an anatomic disfigurement, the male is often advised or chooses to wear a suspensory or skin-tight underwear or both. These devices keep the testes too close to the body and, of course, elevate the scrotal temperature. Hence, poor fertilizing quality of the spermatozoa is produced and maintained. Varicocelectomy by division of the offending veins through an inguinal incision corrects this. Tulloch found improvement in 20 of 30 cases after operation, and Handley reported 11 patients improved after twelve operations. Obviously, such drastic treatment is not indicated unless the wife has been found to be normal.

(To be concluded)

MEDICAL INTELLIGENCE

RUPTURE OF THE ESOPHAGUS*

Report of Two Cases with Atypical Features

HAROLD L. BUSHEY, M.D.†

MEMPHIS, TENNESSEE

RUPTURE of the esophagus was first described by Boerhaave[1] in 1724, and his description of the symptoms is still appropriate today. However, before 1946 there were few reports of this catastrophic event, and no survivors except 2 mentioned by Graham.[2] Since that time, early diagnosis and specific treatment have saved a significant percentage. The importance of early diagnosis and prompt surgery was emphasized by Kinsella et al.,[3] who pointed out that 13 of 53 untreated patients were dead within less than twelve hours of the onset of symptoms, and only 8 survived for at least forty-eight hours. A few have survived for relatively long periods without medical treatment, as in the case reported by Overholt.[4] His patient was first seen eight days after the initial symptoms and eventually recovered completely.

The 2 cases presented below serve to emphasize several points, including the fact that these patients frequently are initially considered medical problems.

CASE REPORTS

CASE 1. A.J., a 46-year-old colored man, was admitted to the Medical Service of this hospital on January 11, 1956, stating that he had been in perfect health until 4 days previously, when he ate "some bad food" and shortly thereafter became nauseated and vomited once. Pain then developed in the upper epigastrium radiating laterally and posteriorly to the left-costovertebral-angle area. This was described as a heavy, constant ache, with an occasional sharp component, and was aggravated by deep breathing. Shortness of breath was progressive and finally forced him to seek medical help. He denied cough, hematemesis, previous chest pain and previous gastrointestinal symptoms. He admitted to a drinking bout approximately 2 weeks before admission.

Physical examination showed a well developed, well nourished man who appeared acutely ill and in respiratory distress. Pertinent findings were limited to the chest and upper abdomen. The chest moved minimally with respiration and inspiratory retraction was noted in the right lower base posteriorly. There was dullness over the right lower half of the chest, both anteriorly and posteriorly. The mediastinum was shifted toward the right. Breath sounds were decreased to absent in the area of dullness. Rales were heard in the right anterior upper chest and in one localized area of the left anterior chest, and scattered throughout posteriorly. The heart rate was regular and rapid; no murmurs were noted. There was minimal tenderness in the left upper quadrant of the abdomen.

The temperature was 101.8°F., the pulse 120, and the respirations 40. The blood pressure was 108/80.

Examination of the blood revealed a hemoglobin of 14.5 gm. per 100 ml. and a white-cell count of 8250 with 86 per cent neutrophils, 13 per cent lymphocytes and 1 per cent monocytes. The sedimentation rate was 17 mm. per hour. The urine gave a + test for albumin, with 10 to 12 white blood cells and 2 to 4 granular casts per high-power field in the sediment. A roentgenogram of the chest taken with a portable machine was interpreted as showing multiple cystic areas with fluid levels in both lung fields, and a questionable effusion on the right (Fig. 1). A thoracentesis on the right yielded 600 ml. of a milky-gray fluid that had a strong fecal odor. A stain of this material revealed gram-negative rods and gram-positive diplococci. The culture subsequently grew out *Escherichia freundii* and *Streptococcus viridans*. Within 24 hours the fluid reaccumulated and a similar fluid was withdrawn.

On January 13 the patient was transferred to the Thoracic Surgery Service, where the possibility of an esophageal perforation was first suggested. Closed drainage was instituted in the left side of the chest and later on the right. Methylene blue was given orally, but none was recovered in the drainage until the procedure was repeated several days later. Subsequently, Lipiodol was given, and the esophageal lesion localized at the diaphragm.

The patient was treated with various antibiotics, which were changed as indicated by sensitivity studies. The course was somewhat stormy, though the temperature rarely exceeded 102°F. On February 29 exploration showed the lesion to be near the cardiac end of the esophagus; this was closed, and an empyema of the mediastinum was drained. Five days later fluids by mouth were tried and appeared in the thoracotomy drainage. Tube feedings were reinsti-

*From the Medical Service, Veterans Administration Medical Teaching Group (Kennedy) Hospital.

†Senior assistant resident in medicine, Crawford W. Long Memorial Hospital of Emory University, Atlanta, Georgia; formerly, junior resident in medicine, Veterans Administration Medical Teaching Group (Kennedy) Hospital.

tuted and continued until April 8, when clear liquids were started. From that point on, the patient's general condition improved steadily, and he was discharged on May 28. At that time a film of the chest was clear except for residual pleural thickening over the right base and an elevated left leaf of the diaphragm. An esophagram revealed a small outpouching at the diaphragm measuring 1 mm. in width and 1 cm. in length.

This patient first sought medical help four days after the initial vomiting. The initial interpretation of the roentgenogram delayed the diagnosis, and it was some time before it was recognized that these pockets with fluid levels were in the pleural spaces.

CASE 2. H.T., a 62-year-old man, was admitted to the Medical Service of this hospital for the 5th time on April 28, 1956. Previous admissions had been for kidney stone, generalized arteriosclerosis, an intertrochanteric fracture of the right femur and a duodenal ulcer with hemorrhage, the last diagnosis being made 17 months before this admission. He had been doing well when last seen about 8 months before admission. Since then he had had occasional bouts of "indigestion," which were treated with alkalis at home. This symptom was further described as high epigastric burning. On the day of admission the patient was nauseated all day. At about 3 p.m. he vomited once about 0.5 liter of material containing blood clots. He was admitted to the hospital at 7 p.m. Neither at that time nor later could a history of pain be elicited.

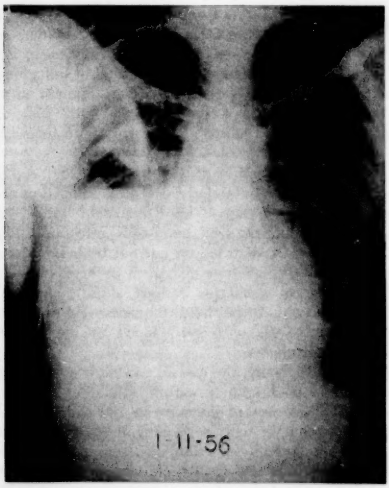

FIGURE 1. *Roentgenogram of the Chest in Case 1 on Admission, Demonstrating Multiple Fluid Levels.*

The patient appeared chronically ill and was slightly confused. The lungs were clear. The heart was unremarkable except for tachycardia. There was moderate epigastric tenderness, but examination of the abdomen was otherwise unrevealing. No blood was recovered from the rectum. The remainder of the physical examination was not remarkable.

The pulse was 130, and the respirations 20. The blood pressure was 160/100.

The hematocrit was 47 per cent, and the hemoglobin 15.2 gm. per 100 ml. Sedatives and atropine were given, and an ulcer regimen including frequent milk and cream feedings and aluminum hydroxide gel was started.

By midnight the blood pressure had fallen to 96/76; the pulse was 140, and the respirations 26. The blood pressure continued to fall and nor-epinephrine (Levophed) was started at 1 a.m. Because of the possibility of gastric dilatation and occult bleeding a Levin tube was passed into the stomach. A moderate amount of coffee-grounds material was obtained, but effected no change in the patient's status. In addition to the nor-epinephrine, 1000 ml. of blood failed to alleviate this acute situation. On the morning of the next day, the situation was judged critical. The hematocrit was now 49 per cent; an electrocardiogram showed only tachycardia. A roentgenogram of the chest was interpreted as showing pulmonary congestion, left-sided pleural effusion and probably an underlying pneumonitis or pulmonary infarction. An abdominal film demonstrated gas in the colon, with no evidence of obstruction. (These films were reviewed later, and evidence of mediastinal and retroperitoneal emphysema was noted.) Physical examination at this time revealed some dyspnea, rales in the left lower axillary area and a pleural friction rub medial to the left nipple. The pulse was 160, and the heart sounds had a ticktack quality.

By noon the temperature had risen to 103°F; the respirations were 48, and the pulse 160. It was necessary to use an intravenous infusion with 12 ml. of a 0.2 per cent solution of nor-epinephrine in 1000 ml. of 5 per cent glucose to maintain a blood pressure averaging 100/70. The patient failed progressively and died at 2:25 p.m. — approximately 23½ hours after the initial vomiting episode.

At autopsy the left and right pleural cavities contained 3000 and 2000 ml., respectively, of a dark-reddish-brown fluid with an aroma of gastric contents. Fibrous exudate was present over the surface of both lower lobes. At the gastroesophageal junction, there was a 2-cm. perforation, with evidence of ulceration at the site of perforation and above it. Dissection extended into the mediastinum and ruptured into both pleural cavities. Also, dissection extended down over the upper half of the stomach, resulting in a grayish, fluctuant bulge to the stomach contour. The peritoneal cavity contained 1500 ml. of a fluid similar to that in the pleural cavity. There was an old healed ulcer in the 1st portion of the duodenum.

The most striking aspect of this case was the absence of pain, in contrast to all previously reported cases.

DISCUSSION

The etiology of rupture of the esophagus may be divided into three groups, as proposed by Anderson[5]: instrumentation or foreign body; neoplasm or long-standing disease; and "spontaneous." The first is becoming more frequent, as in endoscopy and penetrating injuries; this is usually recognized promptly and treated appropriately.[6] The second group includes such conditions as chronic esophagitis, as in Case 2. The "spontaneous" group by definition includes only cases with no pre-existing esophageal disease. Some authors believe that such a rupture cannot happen, and others are just as convinced that it can.[7] Case 1 had no history of pre-existing disease, and the rupture probably occurred at the time of the vomiting. Various investigators have tried to ascertain the pressure necessary to cause rupture. Bódi et al.[8] tried to simulate vomiting in cadavers by the sudden release of controlled pressure via the stomach; they believed that sufficient pressure could be attained in vivo to rupture the esophagus, especially if it was applied rapidly, as in severe vomiting in the presence of a full stomach.

The features suggesting this possibility are: vomiting, severe pain in the chest or upper abdomen, usually on the left, dyspnea, prostration of the patient, subcutaneous or mediastinal emphysema and hydrothorax, or hydropneumothorax. Less important is the apparent association of this condition with peptic ulcer, alcoholism, neurologic lesions, anesthesia and increased intra-abdominal pressures (as with defecation or labor).

Vomiting occurred in both the cases reported above, but is not always present, as illustrated by the 3 cases reported by Anderson.[5] Pain was not severe in Case 1, a stoic patient, and was absent in Case 2, a man previously thought to be hypersensitive to pain. Dyspnea was prominent in both cases. Case 2 demonstrates the rapid deterioration of these patients, and Case 1 is an example of the exceptional stamina occasionally seen. Neither patient had subcutaneous emphysema, though Case 2 had mediastinal and retroperitoneal emphysema unrecognized as such before death. Case 1 had bilateral hydropneumothorax on admission, and Case 2 showed it terminally. Case 2 was known to have had a duodenal ulcer, which, unfortunately, called attention to the obvious, — bleeding ulcer, — and a rupture of the esophagus was not considered.

Both these patients were considered medical problems by the Admission Office. In another case, previously reported from this hospital by Kraeft and Hughes,[9] the patient also was admitted to the Medical Service. This is not unusual. The condition has frequently been diagnosed as myocardial infarction and pancreatitis — pulmonary infarction was considered in Case 2 before death. It is also frequently confused with a ruptured peptic ulcer, and a laparotomy is done before the real problem is suspected.

Once a diagnosis of rupture of the esophagus has been made, prompt therapy should be instituted. If the patient is seen in the first twenty-four hours, definitive surgery is the choice. The shocklike picture is no contraindication, because the patient's condition frequently improves dramatically when drainage of the mediastinum and pleural spaces is established. If the patient is seen in the second twenty-four hours, some authors prefer drainage to thoracotomy. After forty-eight hours there is less need for haste; therefore, it is believed that drainage is the wiser course, definitive surgery being postponed until the patient's condition is more favorable.

Summary

Two cases of rupture of the esophagus are presented; 1 patient survived, and 1 died; both presented atypical findings. The initial roentgenogram in 1 case appeared to show multiple cysts or abscesses. The other patient had no pain.

Diagnosis and therapy are briefly discussed.

References

1. Boerhaave, H. *Atrocis, nec descripti pruis, morbi historia: Secundem medicae artis leges conscripta.* 60 pp. Ludg., Batavia: Boutesteniana, 1724.
2. Editorial comment. In Collis, J. L., Humphreys, D. R., and Bond, W. H. Esophagus. In *The 1944 Year Book of General Surgery.* Edited by E. A. Graham. 736 pp. Chicago: Year Book Publishers, 1944. P. 382.
3. Kinsella, T. J., Morse, R. W., and Hertzog, A. J. Spontaneous rupture of esophagus. *J. Thoracic Surg.* **17**:613-631, 1948.
4. Overholt, R. H. In discussion of Anderson.[5] P. 385.
5. Anderson, R. L. Rupture of esophagus. *J. Thoracic Surg.* **24**:369-388, 1952.
6. Overstreet, J. W., and Ochsner, A. Traumatic rupture of esophagus: with report of 13 cases. *J. Thoracic Surg.* **30**:164-180, 1955.
7. Wachtel, F. W., and Genkins, G. Spontaneous rupture of normal esophagus: report of case with unusual clinical course and pathologic findings. *J. Mount Sinai Hosp.* **22**:6-14, 1955.
8. Bódi, T., Fangor, H., and Forsythe, T. Spontaneous rupture of esophagus. *Ann. Int. Med.* **41**:553-562, 1954.
9. Kraeft, N. H., and Hughes, F. A., Jr. Rupture of normal esophagus: report of case with recovery following unusual complications. *Surgery* **31**:291-296, 1952.

ACUTE BACTERIAL ENDOCARDITIS CAUSED BY *ERYSIPELOTHRIX RHUSIOPATHIAE*

William L. Schiffman, M.D.,* and Asher Black, M.D.†

SYRACUSE, NEW YORK

Erysipelothrix rhusiopathiae, first described by Koch in 1880, was identified by Löffler[1] in 1882 as the causative organism of swine erysipelas. Swine erysipelas affects mainly pigs, but infections with *Ery. rhusiopathiae* occur in other common barnyard animals, such as sheep, horses and fowl. Fish, as well as oysters and lobsters, also can be infected with this organism.

In man the organism can cause erysipeloid, septicemia with arthritis and endocarditis. The erysipeloid form, first described by Rosenbach[2] (1884) is usually a mild, localized cutaneous infection. His description of the skin lesions has not been improved upon. In 1887 he[3] described them as erysipelaslike, slowly progressive, sharply defined, slightly elevated, dark, violaceous, almost livid red zones. He observed that central areas of redness faded as the disease extended peripherally.

Epidemiologically, the disease can be traced to the handling of dead animal matter. Klauder,[4] in 1938, analyzed the source of infection in 100 cases. In all there was contact with dead animal matter. In 58 abattoir workers the infection was from swine; in 16 it was from fish. In 1930 Stefansky and Grunfeld[5] described an outbreak of erysipeloid affecting approximately 200 persons who were cleaners of fish; the disease ran a favorable course in all cases.

Clinically, the incubation period is from one to five days. The disease is confined almost exclusively to the hands, usually at the site of the puncture wound (portal of entry). The important diagnostic feature is the absence of lymphangitis and lym-

*Staff member, Crouse-Irving Hospital.

†Chief, Cardiac Clinic, and chief, Electrocardiographic Station, St. Joseph's Hospital.

phadenitis. These skin lesions disappear spontaneously in five days to six weeks, without desquamation or suppuration.

Heilman and Herrell,[6] in 1944, demonstrated the effectiveness of penicillin as a curative agent in experimental infection of *Ery. rhusiopathiae* in mice. Two years later Barber and Nellen[7] reported that penicillin is the treatment of choice and is an effective one.

Blood-stream infection with *Ery. rhusiopathiae* in man is rare. The first case of such an infection leading to endocarditis proved bacteriologically and at post-mortem examination was described by Klauder, Kramer and Nichols[8] in 1943. In the literature there are no reported cases of cured acute *Ery. rhusiopathiae* endocarditis. However, 1 case of subacute endocarditis cured by penicillin is described by Lawes et al.[9] in the Australian literature.

To our knowledge the following case is the first in the world literature of acute endocarditis produced by this organism that was cured with antibiotic therapy.

Case Report

A 55-year-old construction worker was seen on November 12, 1955, for the chief complaint of muscle pains and fever of 72 hours' duration. Two weeks previously he had fallen from a ladder, injuring his right finger. The injury consisted of abrasion of the dorsum of the finger overlying the proximal interphalangeal joint. During the next few days he worked with land fill, which was later traced to the site of an abandoned pig farm. The injury of his ring finger consisted of a localized swelling with raised edges around a central necrotic area. At the time of examination this wound was undergoing slow resolution and healing. Ten days before he was seen in the physician's office the patient had noticed loss of appetite and increasing fatigue. Seven days later he began having severe muscle pains and also fever; the temperature averaged between 101 and 102° but had been as high as 104°F. On examination there were a small number of petechiae and a heart murmur, which had not been present 3 years previously on a routine examination. Blood cultures taken at the beginning of the examination and 1½ hours later were reported positive within 48 hours for *Ery. rhusiopathiae*, and he was then hospitalized.

The past history was highly suggestive of tuberculous adenitis of the left anterior cervical chain, as indicated by previous incision and drainage on several occasions. There was a small pinpoint residual fistulous opening, with minimal discharge.

The patient reported a daily alcoholic intake of about 4 quarts of beer for many years.

A review of the systems was otherwise noncontributory.

On physical examination the head was symmetrical, with no evidence of trauma. The neck showed a minute draining sinus on the left side. The pupils were round, regular and equal, and the fundi were normal. The ears, nose and throat were not remarkable. The lungs were clear to percussion and auscultation. Examination of the heart showed the point of maximal impulse in the 6th intercostal space 2 cm. to the left of the mid-clavicular line. There was a Grade 3 apical high-pitched systolic murmur and a Grade 2 aortic harsh systolic murmur. No thrills were present. The liver, kidneys and spleen were not felt, and there was no tenderness or masses. Scattered over the trunk and all extremities were slightly elevated lesions varying from 0.5 to 5 cm. in diameter. These were sharply defined, and most of them had paler centers as compared to the darker violaceous peripheral zones. Neurologic examination was not remarkable.

The temperature was 102.2°F., the pulse 120 (and regular in rate, rhythm and force), and the respirations 22. The blood pressure was 130/80.

Examination of the blood showed a hematocrit of 41 per cent, a hemoglobin of 12.5 gm. per 100 ml. and a white-cell count of 10,900, with 83 per cent neutrophils and 17 per cent lymphocytes. The urine had a specific gravity of 1.010, with negative tests for albumin and sugar and occasional epithelial cells in the sediment. Blood cultures on November 12, 14 and 15 were positive for erysipelothrix highly sensitive to penicillin.

An electrocardiogram disclosed a normal tracing, with sinus tachycardia.

The patient was placed on 12,000,000 units of penicillin daily by clysis and streptomycin, 1 gm. daily. The temperature slowly fell from 104°F. on admission to 100°F. 4 days later. It then ranged between 100°F. and 101°F. for the next 3 days. He was subsequently afebrile. This skin lesion gradually disappeared over a 7-day period. At first he noted some mild tenderness about these areas but denied any itching.

Concurrently, over the same period of 1 week, the muscle tenderness subsided. The patient was confused and hallucinated during the 2d and 3d nights in the hospital, but was clear mentally afterwards. The lesion on his finger was healed.

Over the next 4 weeks in the hospital he improved rapidly and was discharged at the end of the 5 weeks after repeatedly negative blood cultures on November 18, 22 and 25 and December 7, 14 and 21. On discharge the apical and basal systolic harsh Grade 2-plus murmurs were still present.

On follow-up examination 3 months later the patient felt well and had no complaints, but because of the persistent murmurs, he was moderately restricted in his activities, pending further cardiac evaluation at the end of a 6-month period. In May, 1956, the murmurs were definitely reduced in intensity, and otherwise a cardiopulmonary review and examination were unremarkable; increased activities were then allowed.

As of November, 1956, this patient was well, without any cardiac complaints. The intensities of the murmurs described were much reduced.

Discussion

A review of the literature reveals many interesting facts concerning this organism. It has been found in many different animal species as either a saprophyte or a pathogen of varying virulence. In the pisces and mollusks it seems to be entirely saprophytic, but in animals, particularly swine, it can gradually or suddenly change into a virulent pathogen. It can lie dormant in contaminated soil for indefinite periods.

In the case described above, the organism apparently survived in the soil for over a year, and then succeeded in contaminating a slight abrasion of the finger.

Nelson[10] claims to have seen more than 500 cases of erysipeloid lesions of the hands in packing-house workers. These were traditionally benign, and good therapeutic results were quickly obtained with penicillin when this became available in 1946.

The development of proved *Ery. rhusiopathiae* septicemia is rare although the literature reveals cases highly suggestive of *Ery. rhusiopathiae* septicemia and endocarditis terminating fatally. Klauder[8] and Russell and Lamb[11] report proved fatal cases of endocarditis, and in both reports there were typical destructive vegetations on the involved valves. In the cases of Russell and Lamb[11] the vegetations appeared to be extremely destructive, and there was

even formation of myocardial abscess. This emphasizes the necessity of early diagnosis and treatment to limit valvular destruction.

We believe that in the case reported above some valvular destruction had occurred early in the disease because of the persistence of the new harsh murmurs.

We are indebted to Miss Winifred Osborne of the Syracuse, New York, City Laboratory for quickly identifying the organism and to Dr. Paul Bunn for bacterial sensitivity tests and assistance in chemotherapy.

References

1. Löffler, F. A. J. Experimentelle Untersuchungen über Schweine-Rothlauf: ausgeführt in der Zeit vom Juli 1882 bis Dezember 1883 im Kaiserlichen Gesundheitsamte. *Arb. a.d. Reichsgndhtsmt.* **1**: 46-55, 1886.
2. Rosenbach, A. J. F. *Mikro-Organismen bei den Wund-Infections-Krankheiten des Menschen.* 122 pp. Wiesbaden: J. F. Bergmann, 1884.
3. *Idem.* Ueber das Erysipeloid und dessen Aetiologie. *Verhandl. d. deutsch. Gesellsch. f. Chir.* Vom. **13** (Part I):10-14, 1887. Ueber das Erysipeloid. *Ibid.* Vom. **13** (Part II):75-79, 1887.
4. Klauder, J. V. Erysipeloid as occupational disease: chairman's address. *J.A.M.A.* **111**:1345-1348, 1938.
5. Stefansky, W. K., and Grunfeld, A. A. Eine Epidemie des Erysipeloids in Odessa. *Zentralbl. f. Bakt.* **117**:376-378, 1930.
6. Heilman, F. R., and Herrell, W. E. Penicillin in treatment of experimental infections due to Erysipelothrix rhusiopathiae. *Proc. Staff Meet., Mayo Clin.* **19**:340-345, 1944.
7. Barber, M., Nellen, M., and Zoob, M. Erysipeloid of Rosenbach: response to penicillin. *Lancet* **1**:125-127, 1946.
8. Klauder, J. V., Kramer, D. W., and Nichols, L. Erysipelothrix rhusiopathiae septicemia: diagnosis and treatment: report of fatal case of erysipeloid. *J.A.M.A.* **122**:938-943, 1943.
9. Lawes, F. A. E., Durie, E. B., Goldsworthy, N. E., and Spies, H. C. Subacute bacterial endocarditis caused by Erysipelothrix rhusiopathiae. *M.J. Australia* **1**:330, 1952.
10. Nelson, E. Five hundred cases of erysipeloid. *Rocky Mountain M.J.* **52**:40-42, 1955.
11. Russell, W. O., and Lamb, M. E. Erysipelothrix endocarditis: complication of erysipeloid: report of case with necropsy. *J.A.M.A.* **114**:1045-1050, 1940.

CURRENT CONCEPTS IN THERAPY*

Sedative-Hypnotic Drugs. III. The Barbiturates — I

THE barbiturates, introduced into medicine by E. Fischer and J. von Mering[1] in 1903, are certainly among the most widely used and abused drugs in medicine. Approximately 400 tons of these agents are manufactured each year; this is enough to put approximately 9,000,000 people to sleep each night for that period if each were given a 0.1-gm. dose.† Over 2500 of these central-nervous-system depressants have been prepared, and out of this large number approximately 60 have been used in medicine. Of these, 16 have had sufficient merit to be described in *New and Nonofficial Remedies*.[2] Undoubtedly, nearly all medical purposes can be served by 5 or 6. With such a wide variety to choose from, it is indeed confusing to the physician in his endeavor to select the most useful agent for his patient. However, nearly all sedation or hypnotic needs can be met with barbital, phenobarbital, amobarbital (Amytal), pentobarbital (Nembutal), secobarbital (Seconal) and the occasional use of hexobarbital (Evipal).

*Prepared under the supervision of the *Journal's* Committee on Advertising.

†From data supplied by Paul de Haen compiled from reports of the U. S. Tariff Commission, 1922-1955.

In this series of compounds it is very important to fit the particular drug to the needs of the patient if best therapeutic results are to be obtained. Although the barbiturates have uses other than that of sedation and hypnosis, this discussion is limited to these aspects. The effectiveness, ease of administration, low cost, widespread therapeutic use and ease of obtaining these drugs by the laity have not only made them among the most useful in medicine but also placed them among the most potentially dangerous agents. As with other powerful agents of nonspecific type, it is essential that the physician know precisely what he intends to accomplish and have a good understanding of the harm that may result from their improper use.

The barbiturates as a class are derivatives of barbituric acid. Substitution of aryl or alkyl groups on the fifth carbon position, exchanging sulfur for oxygen on the second carbon position and substituting a methyl group on the first nitrogen position in barbituric acid result in active preparations. These resulting substances vary greatly in behavior from slow, long-acting agents that are mainly excreted by the kidney to quick, short-acting substances that are entirely destroyed in the body.

The barbiturates are white crystalline powders with a very bitter taste. They are, for the most part, insoluble in water except in the form of their sodium salts. After ingestion they are readily absorbed into the blood stream and widely dispersed in tissue fluids. Depending upon the particular barbiturate, action begins in anywhere from twenty minutes to one hour and may continue for a period of three or four hours to as long as eight to twelve hours. Almost all the barbiturates are metabolized to inactive products in the body, except for phenobarbital and barbital. Approximately 20 per cent of phenobarbital and almost all of barbital are excreted by the kidney. The liver is the chief site of metabolic degradation of the barbiturates.[3] It accomplishes this chiefly by oxidation of the side chain. In the presence of liver disease these drugs have a much more profound effect. Before barbiturates are given, it is important to know the status of liver function; otherwise, serious toxic effects may be produced by what would ordinarily be a relatively normal dose. Furthermore, in the presence of severe renal disease, barbital and phenobarbital should be used much more cautiously.

The chief effect of the barbiturates in the body is, of course, their action as central-nervous-system depressants. This action depends to some extent on the condition of the patient, his level of irritability and his environment at the time when the drug is taken. Sleep produced by the barbiturates is usually dreamless, restful and useful to the patient, and there is not much interference with physiologic activities.

Patients exhibiting Type 2 insomnia, in which a smooth, long-acting sedative is required, respond very well to barbital, 0.3 gm., given as a tablet of the

soluble sodium salt about thirty minutes before retiring. In this group of patients this is often about 8 or 9 p.m. It provides an excellent night's sleep and frequently eliminates the tendency to turn night into day. It seldom produces excitement or other undesirable reactions. When given sufficiently early in the evening there is rarely any effect remaining the next day. Barbital, 0.3 gm., with acetylsalicylic acid, 0.3 to 0.6 gm., or quinine sulfate, 0.3 gm., is a highly satisfactory combination when insomnia is resulting from a combination of aches, pains or restlessness from leg-muscle cramps, joint aches, poor circulation and the tendency to turn night into day.

Patients with much mental tension and especially those inclined to awaken and begin to worry in the early morning hours respond very well to phenobarbital in a dose of 60 mg. to 0.1 gm. at bedtime. Phenobarbital is more of a cerebral depressant than other barbiturates and frequently, perhaps because of this property, creates confusion, excitement and disorientation in elderly persons, especially if there is much cerebral arteriosclerosis. Therefore, its administration in such cases is usually not wise or must be observed carefully if untoward reactions are to be avoided. Phenobarbital has long been a favorite as a mild sedating drug in a dose of 15 to 30 mg. two to four times a day. Although it doubtless does have a beneficial effect in numerous cases when given in this manner, there is a constant need to re-evaluate this type of therapy to make certain that a drug (not a placebo) effect has been created. Phenobarbital given in this manner was certainly the first of the calming or tranquilizing drugs, and when it does not produce sedation, it is still one of the best and certainly the least expensive.

(To be concluded)

References

1. Fischer, E., and von Mering, J. Ueber eine neue Classe von Schlafmitteln. *Therap. d. Gegenw.* **45**:97-101, 1903.
2. American Medical Association Council on Pharmacy and Chemistry. *New and Nonofficial Remedies.* 653 pp. Philadelphia: Lippincott, 1955. P. 324.
3. Maynert, E. W., and Van Dyke, H. B. Metabolism of barbiturates. *Pharmacol. Rev.* 1:217-242, 1949.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42501

Presentation of Case

A thirty-nine-year-old woman entered the hospital because of vaginal bleeding.

The last normal menstrual period occurred five months previously. She missed the next two periods. Two months before admission vaginal bleeding that was associated with abdominal cramps occurred and persisted until the time of entry. One week before admission there was a sudden onset of episodes of stabbing pain in the lower abdomen that was occasionally severe, with radiation to the back. She became nauseated and vomited two or three times. During the four days before entry she noted constipation and dysuria. There was no fever.

The menstrual periods had always been regular, occurring every twenty-eight days. She had never been pregnant. An appendectomy was performed fifteen years previously. Ten years before admission an exploratory laparotomy was performed at another hospital, and tuberculous peritonitis was allegedly found. The postoperative course was complicated by dehiscence of the wound. A cholecystectomy was performed one year later.

Physical examination showed a pale woman in no acute distress. Healed abdominal surgical incisions were noted with a mid-line diastasis in the lower abdomen. There was tenderness in the lower abdomen, with rebound tenderness referred to both lower quadrants. Pelvic examination revealed blood oozing from the cervical os; pain was elicited when the cervix was moved; a tender mass that measured 10 to 15 cm. in diameter was felt in the cul-de-sac.

The temperature was 100.2°F., the pulse 88, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 9.4 gm. per 100 ml. and a white-cell count of 8350. The nonprotein nitrogen was 23 mg., the total protein 7.3 gm., the albumin 4.6 gm., the globulin 2.7 gm., and the bilirubin 0.6 mg. per 100 ml. The prothrombin content was 55 per cent. The cephalin flocculation was negative. The alkaline phosphatase was 3.8 units. X-ray study of the abdomen was negative. X-ray films of the chest were normal except for flattening of the left leaf of the diaphragm in the posteroanterior view.

On the second hospital day an operation was performed.

Differential Diagnosis

DR. MARSHALL K. BARTLETT*: The most inter-

*Visiting surgeon, Massachusetts General Hospital.

esting possibility is whether or not a pregnancy was the cause of this problem. One of the country's leading gynecologists has stated that extrauterine pregnancy is the most common serious pelvic disorder that is diagnosed when it is not present and overlooked when it is. I hope to avoid those errors. What supports or rules out a diagnosis of pregnancy? Obviously, if there was a pregnancy it was not a normal one, but extrauterine. This woman of thirty-nine years had completely regular menstrual periods until five months before admission, when, without any preceding variation in the pattern, she missed two periods. It seems to me that that points to a pregnancy until I can rule it out. At about the time the third period was due she began to have some vaginal bleeding, with crampy abdominal pain, that persisted until the time of entry. That, too, is compatible with an extrauterine pregnancy, although it is not entirely typical. I am interested in the hemoglobin level of 9.4 gm. per 100 ml. She had been having spotty vaginal bleeding for two months; we are not told how much. It would take a fairly substantial amount of vaginal bleeding over a two-month period to reduce the hemoglobin to that level; therefore, I wonder whether it may have been related in part to the recent episode in the week preceding admission, which may have involved intra-abdominal bleeding. Clearly, there was not rapid bleeding on admission; the vital signs were stable, and there was no problem of hemorrhage. I wonder, however, if there had been bleeding into the peritoneal cavity as well as vaginal bleeding during that week before admission.

The white-cell count was normal. Bleeding into the peritoneal cavity usually causes an elevation of the white-cell count, but that may return to normal in twenty-four or forty-eight hours, so that I do not think that rules it out. Likewise, the modest elevation of the temperature is consistent with it. Nothing about the cervix or uterus, other than blood coming from the cervix, was recorded. It would be interesting to know whether the cervix was normal or was softened and whether the fundus was normal or enlarged. The fundus should, of course, be somewhat enlarged with an extrauterine pregnancy. The finding of a tender pelvic mass is certainly consistent with ectopic pregnancy.

What are the points against extrauterine pregnancy? The record did not state how long the patient had been married or how much exposure to pregnancy she had had. Failure to become pregnant over a period of years would decrease the chances of a pregnancy as the cause of this problem. Also, she was said to have had tuberculous peritonitis some years previously, and the incidence of pregnancy after tuberculous peritonitis is very low. The history was too long for the usual ectopic pregnancy. Such persons usually miss one period and, before or about the time of the second period, begin to have vaginal staining. Shortly thereafter the situation becomes acute because of intra-abdominal bleeding. If I am going to persist in my thought that this was an extrauterine pregnancy, I have to explain that history in some way. Then, to explain a mass of this size, I should have to assume that the conceptus was extruded from the tube without killing it or destroying its blood supply and that it became a secondary abdominal pregnancy or that it was a primary abdominal pregnancy that went on to this stage. Those are both rare situations. If one of them did occur, there would then be a mass with subsequent bleeding into it, such as was described. The mass described was considerably larger than the usual extrauterine pregnancy; this increase in size must have been related to hemorrhage in and about it. Another point, perhaps a small one, is that there was no note about symptoms of early pregnancy, which may be present in an extrauterine pregnancy. Thus, there are a certain number of points favoring the diagnosis and a number of fairly strong points against it.

What else could this have been? I suppose that it could have been something unrelated to the pelvic organs, but I think this creates an even more unlikely situation. The appendix was removed. Could the patient have had a neoplasm of the sigmoid? It is possible, but then I should have to assume that it had become inflamed by virtue of perforation. She had no symptoms of disease in the bowel except during the four days before admission, so this seems unlikely. Could it have been diverticulitis? She was somewhat young for this disease. It occurs at that age much less commonly than it does in females somewhat older. Again, she had no background for it; she had no previous attacks and no changes in bowel habits except for the immediate ones. I should think that that would be unlikely.

What diseases related to the pelvic organs must I consider? Salpingitis is one, and because of the story of possible tuberculous peritonitis, I should include tuberculous salpingitis. This condition can be associated with menstrual irregularity. I do not think it is so often associated with this kind of menstrual irregularity — sudden cessations of periods that have been previously entirely normal — as pregnancy, but I certainly cannot rule it out on that basis. I think, therefore, that I have to accept an enlarged and inflamed tube as a possibility but not as a likely one.

Endometriosis, with leakage from an endometrioma as the cause of the acute symptoms in the week preceding admission, is another pelvic disorder that must be considered. The history was short for that. There was no history of abdominal discomfort in the two months before admission — no dysmenorrhea; I do not see anything in favor of endometriosis, although this woman was a good candidate for it, being nulliparous and thirty-nine years of age.

A fibroid arising from the uterus, with interference of its blood supply, is a possibility. I cannot rule that in or out, nor can I exclude an ovarian cyst, with a twisted pedicle and interference with its blood supply.

I cannot exclude any of the possibilities I have

mentioned; I suppose statistically several are more likely than extrauterine pregnancy. Nonetheless, I think that I shall make as my diagnosis an extrauterine pregnancy.

DR. JACOB LERMAN: I should like to ask Dr. Bartlett if he would consider a functioning type of ovarian tumor with functional uterine bleeding—a granulosa-cell tumor, for example.

DR. BARTLETT: I think that is certainly a possibility; I see no way of ruling it out.

DR. WINFIELD S. MORGAN: Dr. Curtin, would you like to comment?

DR. RICHARD R. CURTIN: Our opinion on the Service was that the patient probably had a tuberculous salpingitis. We considered pregnancy, but she had had tuberculous peritonitis and had been married for nineteen years without becoming pregnant. Our first diagnosis was tuberculous salpingitis, and the second was extrauterine pregnancy.

CLINICAL DIAGNOSIS

?Tuberculous salpingitis.
?Extrauterine pregnancy.

DR. MARSHALL K. BARTLETT'S DIAGNOSIS

Extrauterine pregnancy.

ANATOMICAL DIAGNOSIS

Tubal pregnancy.

PATHOLOGICAL DISCUSSION

DR. MORGAN: Dr. Curtin, will you describe the operation?

DR. CURTIN: Operation showed an extrauterine pregnancy in the fimbriated end of the right tube, which was not bleeding significantly at the time that we explored the abdomen. There was a rather large hernia that had resulted from the previous laparotomy. We repaired that.

DR. MORGAN: How much blood was there in the pelvis?

DR. CURTIN: There was only a small amount of old blood.

DR. ALFRED KRANES: How old was the pregnancy?

DR. CURTIN: It must have been several months. We learned later that the dilatation and curettage performed at another hospital six weeks before admission was said to have shown decidual tissue. We had been told by the referring physician at the time of admission that the curettings had given no signs of pregnancy.

DR. BARTLETT: How large was the mass?

DR. CURTIN: It was about 5 cm. in diameter and quite movable by pelvic examination under anesthesia.

DR. BARTLETT: That size is more in keeping with the usual extrauterine pregnancy.

DR. CURTIN: Yes; it was about the size of a six-weeks' pregnancy and had remained at about that size for several months, as nearly as we could tell.

DR. MORGAN: The specimen that we received in the laboratory was a tube measuring about 10 cm. long, in the distal portion of which there was a fusiform swelling about 6 cm. in diameter. When that was sectioned a great deal of hemorrhage and a small, cystic cavity about 2.5 cm. in diameter were encountered. The microscopical sections showed placental villi and also a considerable amount of chronic inflammation and fibrosis. I think that it was very likely that the patient had had some chronic salpingitis in the past, resulting in scarring and changes that interfered with passage of the ovum through the tube and the subsequent development of the pregnancy there.

CASE 42502

PRESENTATION OF CASE

A sixty-five-year-old woman entered the hospital because of weakness of the legs.

Three weeks previously she noted the gradual onset of an ache in the lower portion of the back that subsided after three days. There was no history of trauma. Subsequently, there were persistent, crampy pains in the calves that were worse on the right side and an inability to climb stairs because of weakness of the legs that was worse on the left side. Coughing made the pain in the right leg worse. Numbness of the lateral aspect of the left calf and the left foot was also noted. Two weeks before admission the weakness of the legs had progressed, so that she could not walk. She was admitted to another hospital, after which a slight return of strength in the right leg occurred. A lumbar puncture yielded cerebrospinal fluid with a total protein of 213 mg. per 100 ml. Five days later there was severe pain in the lower portion of the back that was associated with numbness of the lateral aspect of the left leg. At the same time she noted that she was unaware of sensation in the urinary bladder and voided involuntarily.

A panhysterectomy was performed eleven years before admission because of an adenocarcinoma of the uterine fundus and a dermoid cyst of the right ovary.

Physical examination showed a well nourished woman in no distress. The urinary bladder was distended with urine. Neurologic examination revealed an area of hypesthesia and hypalgesia over the anterolateral aspect of the left leg that extended over the medial portion of the dorsal aspect of the left foot and included the great toe. There was a foot drop on the left, with almost total inability to dorsiflex and evert. A lesser degree of weakness of the same muscle groups was noted on the right side. Straight-leg raising to 75° caused pain in the calves that was greater on the right side. The upper abdominal reflexes were active; the lower abdominal reflexes were absent. The deep tendon reflexes were brisk and more

active in the weaker leg. There was ankle clonus on the left side. The plantar response was flexor bilaterally. Rectal examination showed a relaxed sphincter. Pelvic examination was negative.

The temperature was 99.4°F., the pulse 102, and the respirations 20. The blood pressure was 140 systolic, 90 diastolic.

The urine gave a + test for albumin; the sediment contained 6 white cells, an occasional hyaline cast and a few bacteria per high-power field; a culture grew out abundant alpha-hemolytic streptococci. Examination of the blood revealed a hemoglobin of 13.8 gm. per 100 ml. and a white-cell count of 13,300, with 75 per cent neutrophils. An x-ray film of the chest was normal except for cervical ribs bilaterally. Films of the thoracic spine were also normal. Films of the lumbar spine and pelvis demonstrated fusion of the anterior portion of the bodies of the first and second lumbar vertebras; the pedicles of these vertebras were thinned, with widening of the interpedicular space; moderate degenerative changes were noted in the remaining lumbar vertebras; there was some narrowing of the right side of the interspace between the fourth and fifth lumbar vertebras (Fig. 1).

A lumbar puncture between the third and fourth lumbar vertebras yielded clear, colorless cerebrospinal fluid with normal dynamics; it contained 8 neutrophils and 9 lymphocytes per cubic millimeter; the total protein was 54 mg. per 100 ml. A lumbar myelogram demonstrated unusual widening of the subarachnoid space in the lumbar region; the contrast substance went from the lower lumbar level up to the fused first and second lumbar vertebras, where there was a complete block and cupping of the contrast material. A second myelogram (Fig. 2), with injection of the contrast medium into the subarachnoid space through the cisterna magna, demonstrated a block at the upper border of the first lumbar vertebra; a convex defect was seen at this level, where the pedicle of the first lumbar vertebra was widened; the total protein of the cisternal fluid was 23 mg. per 100 ml.

An operation was performed on the fourth hospital day.

A B

FIGURE 1. *Anteroposterior and Lateral Views of the Upper Lumbar Spine, Showing Congenital Fusion of the First and Second Lumbar Segments and Pressure Erosion of the Medial Aspect of the Pedicles, Particularly of the First Lumbar Vertebra (Arrows).*

DIFFERENTIAL DIAGNOSIS

DR. LOUIS BAKAY*: Before looking at the x-ray films I shall discuss the localization and the possible nature of this lesion. My discussion is made somewhat easier by the myelographic findings that point to a space-taking lesion in the spinal canal between the first and second lumbar vertebras. The patient's inability to climb stairs indicates that several muscle groups — the iliopsoas and the quadriceps and extensor muscles of the thigh — were involved. The iliopsoas muscle gets its innervation mainly from the first lumbar segment, the adductor muscles of the thigh from a lower segment, and the quadriceps mus-

*Assistant in neurosurgery, Massachusetts General Hospital.

cle from the third to the fourth lumbar segment of the spinal cord. The numbness of the anterolateral aspect of the left leg and foot, as well as the foot drop on the left, with inability to dorsiflex and evert, is also evidence of interference with the fifth lumbar segment. The unawareness of sensation in the urinary bladder and the involuntary voiding may have been caused by lesions of the first and second sacral roots, or by lesions higher up, including the posterior columns of the spinal cord. The absence of the lower abdominal reflexes points to interruption of the reflex arc at the lowermost thoracic or the uppermost lumbar segment. The ankle clonus is an interesting finding, but it is difficult to establish how much injury there was to the pyramidal tract because of the flexor plantar reflex. In summary, the patient's complaints indicate irritation or paralysis of most of the lumbar nerve roots and, possibly, interference with the second and third sacral roots.

There was a fairly rapid onset with a duration of only three weeks from the first symptom to a very advanced paralysis; yet in contradistinction the x-ray findings seem to indicate that there was a long-standing, or even a congenital, lesion. I do not believe a fusion of the first and second lumbar vertebras could have occurred recently. Although a tumor can widen the spinal canal, it takes some time to do so; three weeks would not be enough for such widening to take place. There was a certain change and slight remission in the clinical picture. The findings were first predominantly on the left side; later, they were also on the right side. There was improvement, although the course generally was steadily downhill. The variation and improvement in the symptoms suggest that the lesion may not have been solidly fixed inside the spinal canal and possibly, with the motion of the patient or as a result of hydrodynamic changes, pressed on roots, sometimes on one side and sometimes on the other. Gradually, it involved more and more roots.

A B

FIGURE 2. *Intradural Lesion Outlined in the Myelograms. The upper edge of the lesion is shown in* A *(arrow), and the lower edge in* B.

Of interest are the findings in the spinal fluid. At one time the total protein was 213 mg. and later it was 54 mg. per 100 ml. Also, the dynamics were normal, and the fluid at the second lumbar puncture was not xanthochromic and contained a normal amount of protein; yet there was a complete defect above the level of the lumbar puncture on the myelogram. We know that there may be a complete spinal defect with a space-taking lesion of the spinal cord shown in the myelogram, whereas the dynamics are free because a 1-mm. or 2-mm. communication between the spinal column above and below the tumor is enough to ensure normal hydrodynamics but not large enough to allow more viscous material to flow through it. The facts that there were signs of a compression syndrome with a high cerebrospinal-fluid protein, and later that there were not, and that there were normal dynamics and yet a complete block noted

in the myelogram make me wonder whether the tumor was floating, plugging the canal completely at times and leaving a small passage for the spinal fluid at other times.

From the clinical symptoms it is difficult to decide from which structure the lesion originated. It is difficult to place because it lay between the first and third lumbar vertebras at the point where it compressed the roots of the cauda equina, as well as the lowermost portion of the conus of the spinal cord. In such cases one can almost always find signs of involvement of both these structures. It may have arisen from the conus or the filum terminale and involved the fibers of the cauda equina afterward, or it may have started from one fiber in the cauda equina and compressed the cord afterward. The shortness of the clinical history favors a lesion of the conus medullaris; the early involvement of the urinary bladder favors a lesion in the filum terminale or the lowermost portion of the conus but does not exclude a primary lesion of the cauda equina. Most of the lesions that arise in the conus or cauda equina also involve by pressure the lowermost portion of the spinal cord and usually cause a flaccid paralysis of the legs, with fasciculations. There was no history in the case under discussion of muscular fasciculations in the legs; moreover, the muscles of the leg were not flaccid but spastic, as demonstrated by the ankle clonus. On the other hand, there was no mention of the reflexes, which I assume means that the ankle and knee jerks were equal and normal, and both plantar reflexes were flexor. These findings are more frequent with lesions of the conus than of the spinal cord just above it or of the cauda equina.

There was some evidence of infection. The patient, although she did not have a temperature, had a high pulse rate, a somewhat increased white-cell count and some infection in the urinary bladder. The temperature and white-cell count could be explained by the infection in the bladder, but I am at a loss to explain the 8 neutrophils per cubic millimeter in the cerebrospinal fluid because there was no other sign pointing to infection of the spinal fluid. Before I discuss the types of lesion, may I see the x-ray films?

DR. JOSEPH HANELIN: There is fusion of the first and second lumbar bodies, nearly complete, even posteriorly, although there is a small radiolucent cleft at the expected position of the disk (Fig. 1). This type of fusion is typical of a congenital lesion as opposed to one that resulted from old infection. The other finding of interest consists of changes involving the pedicles of the first and second lumbar segments; there is distinct widening of interpedunculate spacing and evidence of pressure erosion upon the medial aspects of the pedicles, particularly of the first lumbar vertebra, although the second lumbar vertebra also seems to be involved. The bone is otherwise healthy; there is no lytic or cancerous lesion. The x-ray findings are consistent with an intradural space-taking lesion partially at the level of the conus and partially below it that over a long period has produced erosion of the bony spinal canal.

DR. BAKAY: In the differential diagnosis of a space-taking lesion I shall start with the less likely possibilities. The space-taking lesion in the lower portion of the spinal canal could be a ruptured intervertebral disk, a tumor or a granuloma, infectious or parasitic. The last possibility is remote. Nor is a ruptured intervertebral disk likely, because at this patient's age and in this high an interspace it is a rare lesion. Moreover, those lumbar vertebras were fused, with practically no interspace and practically no disk between them.

The most likely possibility is tumor. The patient had a panhysterectomy eleven years before admission because of a cancer of the uterine fundus; however, the pelvic examination now was negative. Eleven years is a long time for an adenocarcinoma of the fundus, which is not a very malignant condition, to remain latent; so that on a historical basis she probably did not have a metastatic tumor of the spine. Moreover, the tumor was rather round and well encircled, did not involve many segments and seemed to be inside the canal, not particularly attached to the dura.

I am left with the group of spinal tumors proper. In the area of the conus and the uppermost level of the cauda equina the statistical likelihood of tumors is different from the statistical likelihood elsewhere in the spinal cord. Naturally, neurofibromas are as common here as elsewhere and frequently involve all the fibers of the cauda equina. It seems to me that if this were a solid neurofibroma of the caudal roots, the duration from the first sign to almost complete disability would have been longer. The same argument would be valid for another tumor appearing frequently in this region, the meningioma.

Some tumors, however, occur more frequently in this area than elsewhere in the spinal canal; chief among these are gliomas of unclassified nature. As a matter of fact, sometimes they remain unclassified; sometimes, they are varieties originating in various glial formations. Of these, ependymomas are probably more frequent in this area than in other parts of the spinal cord. Sometimes, the ependymomas have the usual histologic character, and sometimes they are pseudomyxomatous. Sometimes, they are relatively slowly growing; sometimes, they are malignant and even erode the sacrum. The fact that there was an underlying congenital abnormality — namely, fusion of the vertebras and widening of the spinal canal — may or may not be of significance. A tumor may have been present for quite a long time and yet may have caused symptoms only three weeks before admission. Sometimes, soft-tissue tumors, gliomas and ependymomas in particular, can fill out the caudal portion of the spinal canal almost completely and yet interfere very little with the caudal fibers until the pressure becomes too great. The myelographic picture is not consistent with that possibility.

Another possibility is dermoid cyst. Epidermoids are more frequent in the area of the conus than in other parts of the spinal cord. They are small, rounded lesions, very much like the one described. They are usually attached rather loosely to the filum terminale or to the caudal roots and move around considerably, compressing sometimes one root and sometimes another and causing a great variety of symptoms. They also grow slowly and may very well be associated with congenital fusion and widening of the spinal canal.

I think the only diagnosis that I should dare make is intradural tumor of the first and second lumbar area, possibly a glioma or possibly an epidermoid cyst, or a neurofibroma, in that order.

Clinical Diagnosis

Intraspinal tumor, opposite first and second lumbar vertebras.

Dr. Louis Bakay's Diagnosis

Intradural tumor, first and second lumbar area, ?glioma, ?dermoid cyst.

Anatomical Diagnosis

Teratoma, first and second lumbar area.

Pathological Discussion

Dr. Edward P. Richardson, Jr.: Dr. Bakay has given us an excellent discussion of the possibilities to be considered in a case of this sort. The diagnosis he arrived at — a neoplastic lesion at the level of the first and second lumbar vertebras — is essentially correct. Dr. Jost J. Michelsen, in doing a laminectomy at the first and second vertebras, immediately was aware of the presence of an intradural, rounded mass. On opening the dura he noted a plum-shaped, yellow, cystic tumor that evidently was clearly attached to the spinal cord. With a needle and syringe he was able to aspirate yellow fluid from this. He sent a portion of it over to us for frozen section, and some epithelial cells were seen that led to an erroneous diagnosis of a malignant tumor. He was surprised at the report, in view of the innocuous appearance of the lesion, and removed all he could of the tumor. He could not remove the lesion completely because he would have had to sacrifice the conus medullaris, which was clearly involved by the tumor. Further study of the tumor in permanent sections revealed that it was an odd one, made up of various tissue types. There was much well differentiated epithelium of differing sorts — some of it stratified squamous, closely resembling epidermis, and other portions of it columnar, with clearly visible cilia in places. Scattered about were irregular islands of glial tissue, made up of mature astrocytes and their fibers. The tumor contained a considerable amount of collagenous connective-tissue stroma. Because of the clearly differing sorts of epithelium in the tumor, together with glial islands, we believe that this was a teratoma, even though many of the tissue structures that one may find in a teratoma — such as bone, muscle, intestinal epithelium and cartilage — were absent. The tumor in no way resembled ependymoma.

This is an extremely rare tumor of the spinal cord and is the first case of the kind that we have had here. Typically, these tumors are found dorsal to the cord; they may be intradural or extradural. By far the majority are found in the lumbosacral region. These tumors are related to the epidermoid or dermoid cysts of this region, which are somewhat more frequently encountered. Reviews of the subject are those of Bucy and Buchanan[1] and Henschen.[2]

Dr. Reed Harwood: Did the patient make a good recovery?

Dr. Richardson: She made a good recovery and has been discharged from the hospital.

References

1. Bucy, P. B., and Buchanan, D. N. Teratoma of spinal cord. *Surg., Gynec. & Obst.* **60**:1137-1144, 1935.
2. Henschen, F. Tumoren des Zentralnervensystems und seiner Hüllen: spinale Teratome. In *Handbuch der speziellen pathologischen Anatomie und Histologie*. Edited by O. Lubarsch, F. Henke and R. Rössle. Vol. 13 (Part 13). 1098 pp. Berlin: Springer-Verlag, 1955. Pp. 872-875.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

OWNED BY THE SOCIETY AND
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
Oliver Cope, M.D. James M. Faulkner, M.D.
Richard E. Alt, M.D. Conrad Wesselhoeft, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Robert O'Leary, ASSISTANT EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. J. Englebert Dunphy, M.D.
Dwight O'Hara, M.D. Robert W. Buck, M.D.
Fletcher H. Colby, M.D. Herrman L. Blumgart, M.D.
Robert L. Goodale, M.D. Frank N. Allan, M.D.
Chester M. Jones, M.D. Harvey A. Kelly, M.D.
Harvey R. Morrison, M.D. Langdon Parsons, M.D.
Maxwell Finland, M.D. Mark Aisner, M.D.
Vernon P. Williams, M.D. Dale G. Friend, M.D.
Benjamin Castleman, M.D. Richard Warren, M.D.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal. The *Journal* does not hold itself responsible for statements made by any contributor.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

COPY for advertisements is accepted by the advertising committee of the *Journal* on the basis of the apparent quality and usefulness of the product and the manner of its presentation. Proprietary names of pharmaceutical products must be accompanied by the chemical, or generic or official names, and the quantity of all active substances and the recommended dose must be stated. Copy should be factual, conservative and in good taste.

ALTHOUGH it is believed that all advertising material accepted conforms to ethical medical standards, acceptance does not imply endorsement by the *Journal*.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (residents, interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

"GREAT MEDICINE"

TIMED, possibly, to coincide with the presentation of a special Albert Lasker Award to Dr. Alan Gregg during the meetings of the American Public Health Association last month, Columbia University Press has released his new book, *Challenges to Contemporary Medicine*. This text is a putting into print of the five American Bampton Lectures — they have their British counterparts — delivered by Dr. Gregg at Columbia in 1953 under the specific titles "How Dear Is Life," "What Is the Meaning of Disease," "Current Factors Affecting Medicine," "How Are Medical Education and Care Paid For" and "The Natural History of the Doctor."

In these five lectures, comprising the five chapters of his challenging book, Dr. Gregg, recently retired as vice-president of the Rockefeller Foundation and director of its Division of Medical Sciences, expounds the concept and develops the practical significance of "Great Medicine." Great Medicine, according to this concept, is the whole of medicine in all its aspects, based on the advancement of precise and dependable knowledge, and it is today one of the most complex and vital services that mankind is asking man to deliver. To understand its meaning in any country one must study its historical, social, cultural, economic and scientific matrix; within Great Medicine is included the teaching, the practice and the research in medicine, in all its roots and branches.

In view of the prevalent misunderstanding of the values and economy of Great Medicine in relation to other aspects of life, Dr. Gregg's lectures are a plea not merely for the acceptance of his evaluation but for its general support by the most logical means. For there is still lacking a general appreciation of the value of medical care in relation to its cost, and there is still needed a realization that the cost of medical education and of medical research is part of the cost of medical care, for which universities are now being penalized.

Parenthetically, Dr. Gregg agrees with many other observers that the three components of prosperity — leisure, wealth and power — are not an answer to the affliction of adversity but a problem in themselves, in that man has not yet acquired the knowledge of what to do with them after he has them. Relative prosperity for considerable numbers of population is still a new experience in the history of man, and at present the survival of prosperity constitutes a more serious problem than the survival of adversity.

If the costs of health are compared with other costs of living such as new hats and clean shirts, which are accepted not uncheerfully, they can scarcely be considered exorbitant nor are they beyond the reach of the average citizen when put on a voluntary prepayment basis. Since the likelihood of the need of health services is becoming "calculable for large numbers," it is consequently adaptable to insurance procedures, which are already being applied to it in a large way.

There is implied no threat to the private practice of medicine for those who wish to receive their medical care in the orthodox fashion, but only broader opportunities for a more practical economy in paying for it.

MAINTAINING THE CRITICAL ATTITUDE

THE physician may be forgiven if he tends to forget that his has not always been a success story. There have been setbacks, big and little, as well as the celebrated victories of medical progress, and there remain failures today — of leukotomy to live up to its heralded promise, and of cortisone really to "cure" arthritis, to mention but two. And yet if reference is made to accounts of medical history the record appears so steadily pleasing that the heirs to all the gains can justly glow with the satisfaction of a job well done. The isolation of infectious agents and control of so many of the communicable diseases, the birth and fruition of biochemistry, pharmacology and antibiotic medication; the great advances of surgery, roentgenology, ophthalmology and the other specialties are tangible and lasting accomplishments. Appendectomy, ether, pernicious anemia, penicillin, vitamins, hookworm, malaria — the very names are like place names of history that are synonymous with victory.

But if there have been Jenas there have also been Waterloos. And it is salutary — as salutary as the clinicopathological conference or the report of a committee on maternal welfare such as that published in this issue of the *Journal,* which publicizes a fatal reaction from an incompatible blood transfusion — that the defeats should not be lost to sight in the glare of yesteryear's glory. The conquest of puerperal sepsis was slow because of stubborn, vindictive resistance to the appreciation of the fact that physicians may spread disease as well as heal it. Of recent memory and perhaps more instructive on that account has been the creation, so to speak, of new diseases on those rare occasions when medical procedures or new medications have resulted in such conditions as agranulocytic angina, postirradiation leukemias, retrolental fibroplasia, acute yellow atrophy of the liver, transfusion reactions — and doubtless other uncommonly seen and slowly developing illnesses not so readily recognized as the tight little list of examples given.

At least it is certain that at times a boomeranging therapy may result in metabolic conditions of uncertain pathogenesis, as uncertain as the arthus phenomenon and periarteritis nodosum, and they may be as ominous as cancer or as banal as hives. The physician may be forgiven if he tends to forget this and for overlooking the obscurely defined syndrome in which he may play an unwitting role. For at the very time when "iatrogenic" diseases are emerging they are usually being recognized. And in that event attempts are usually already under way to rectify, minimize and prevent them. On the other hand, there are times when the pros and cons of therapy are reasonably well defined, and, notwithstanding, an error is made. As the Committee on Maternal Welfare views the particular case "it seems only honest and fair that the responsible physician should share . . . the onus for the mistake" when he has made one. But how can he assume the onus for a mistake when he does not even know he has made one?

Another article in this issue of the *Journal,* the Medical Progress report, points up the so largely jumbled status of applied endocrinology — the giving of injections without adequate controls, the expression of results and claimed results without objective criteria for their evaluation or testing of their significance. And what is more pertinent to the point being made here, no provision is made for the evaluation of harm — after injection of testosterone, for example. The assumption is usually taken for granted that if it fails to restore fertility it will do no harm. Likewise, hormones are administered again and again for infertility, and no doubt in some cases after infertility has given way to pregnancy, without later evaluating pathogenic potentialities or possible teratogenic impact on the fetus.

In concluding his own progress report Simmons quotes from that of Friend and McLemore published earlier in the *Journal* on "Some Abuses of Drugs in Therapy." Their point needs to be made again and again.

> It is essential that the physician . . . maintain a critical attitude concerning all preparations until they have demonstrated their merit by satisfying the rigid demands of critical investigators, careful observers and, perhaps as important as the former, the test of numbers and time . . .
>
> Unfortunately, these factors [undesirable effects and toxicity] combined with confusing terminology and complicated dosage patterns have made it nearly impossible for the average physician to understand completely and to employ wisely some of the more useful preparations. Consequently, certain abuses have developed that not only are undermining confidence in drug therapy but also can be harmful to the patient. . . .

MANAGEMENT OF ILEOSTOMIES

Two years ago a special article on the mutually supportive activities of a group of ileostomy patients was published in the *Journal.** The organization and functions of this group, now of four years' standing, were described as well as the derivation of the somewhat cryptic name, selected not primarily because the group met and operated on the quiet, but rather in reference to Wards Q and T of Mount Sinai Hospital in New York, among whose patients a similar association had already developed.

In order to further its work and give it as wide currency as possible, QT Incorporated of Boston has

*Lenneberg, E. QT Boston — ileostomy group. *New Eng. J. Med.* 251:1008-1011, 1954.

already in these few short years published three editions of its *Manual for Ileostomy Patients,* which frankly removes any suspicion of undesirable reticence from the problems attendant on ileostomies.

The *Manual* is divided into three sections of which the first, consisting of brief articles by a number of authorities, both lay and medical, provides necessary background material for the person destined thereafter to make his or her peace with this anatomic alteration. In this section the mechanical disadvantages and the psychic hazards of living with an ileostomy are described, with comforting emphasis on the ability of those who make the adaptation to lead normal, actively participating lives.

The second section comprises a practical manual of technics in management, with recognition of the fact that each ileostomy and each patient represent an individual experience as regards both the type of apparatus to be employed and the methods of using it. Other practical aspects are taken up in the final section. These apply to domestic relations and the bearing of children; to business; to recreation, even including swimming; and to travel. They include considerations of costs of equipment, of deduction of medical expenses for income-tax purposes and of aspects of insurance coverage.

The *Manual* is something of which every physician dealing with these cases should be aware; for the bearer of an ileostomy stoma it is a *vade mecum.*

PROFESSOR MARTHA MAY ELIOT

THE Harvard School of Public Health, sharing honors with the new professor herself, is to be congratulated on the appointment of Dr. Martha May Eliot as head of its Department of Maternal and Child Health. In succeeding Dr. Harold C. Stuart, who has directed the Department since it was founded in 1927, Dr. Eliot will become, with Cora Du Bois of the Department of Anthropology, and Cecelia Payne-Gaposchkin, professor of astronomy, one of three women with full professorships at the University.

The appointment caps a distinguished career. A graduate of Radcliffe College in the Class of 1913, Dr. Eliot engaged in social service for a year before entering Johns Hopkins Medical School, from which she graduated in 1918. She interned at Peter Bent Brigham, St. Louis Children's and Massachusetts General hospitals, and then joined the staff of Yale University Medical School.

Her association with the Children's Bureau began in 1924, as a staff member; in 1941 she became associate chief of the Bureau, and in 1951 its chief. In 1947 she was elected the first woman president of the American Public Health Association and in the same year became assistant director general of the World Health Organization. Among the various honors that have been conferred on Dr. Eliot have been degrees from Rochester, Yeshiva and Boston universities, Smith, Wheaton and Mt. Holyoke colleges, the University of Colorado and Women's Medical College.

In returning to New England Martha Eliot is bringing her talents home again, for she was born in Dorchester in 1891, the daughter of a Unitarian minister. A descendant of President John Adams, she is more currently a sister of Rev. Dr. Frederick May Eliot, for many years head of the American Unitarian Association, and of Abigail Eliot, founder of the Boston Nursery Training School.

In order to ascertain whether a medicine is prophylactic against a contagious disease, we must first ascertain whether the subjects for experiment are capable of taking it; in other words, whether they have ever had it. Next, the patients must be equally exposed to the source of contagion; and lastly, the drug must be given to a certain number only of those so exposed.

Boston M. & S. J. *December 18, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

REACTION FROM INCOMPATIBLE BLOOD TRANSFUSION

A twenty-one-year-old woman died in Massachusetts sixteen days after a cesarean section in another state during the thirty-eighth week of her third pregnancy.

During her first pregnancy, at the age of eighteen, the Public Health Department laboratory of her home state reported the blood as Group A, Rh negative. During the second pregnancy she was admitted to the hospital for severe anemia and was given a transfusion. The hospital laboratory reported the Blood as Group A, Rh positive, with no agglutination in major and minor crossmatching, and there was no reaction.

At eight and a half months in the current pregnancy, sudden, profuse vaginal bleeding necessitated hospitalization, after she had been seen only once prenatally, at twenty-four weeks. Admitted at noon with a hemoglobin of 10.8 gm. per 100 ml., she was operated on at 4 p.m. for placenta praevia. A hydropic baby, which died shortly thereafter, and placenta praevia were found. Blood loss during the operation reduced the hemoglobin to 6.4 gm. per

100 ml., and at 6:20 p.m. the patient was given a transfusion of 500 ml. of type A, Rh positive, blood from the same donor who had given her blood without a reaction in her second pregnancy. Again, her blood group was found to be A, Rh positive, and both major and minor crossmatchings were said to be satisfactory.

On the next day lumbar pain, hemoglobinuria and oliguria developed. She became completely anuric on the second postoperative day, the nonprotein nitrogen rising to 101 mg. per 100 ml., and she was transferred to a Boston hospital for dialysis.

On admission she was drowsy and febrile and had a pulse rate of 110. There were signs of fluid at the left-lung base with right-costovertebral-angle tenderness. Urinalysis gave a + + + test for protein, with granular and hematin casts in the sediment. The blood urea nitrogen was 70 mg. per 100 ml. on admission, and the blood was found to be Group A, Rh negative.

Progressive uremia, acidosis and hyperkaliemia developed. Convulsions occurred, and in a week she was dialyzed on the artificial kidney. This restored her chemically toward normal, but, after dialysis, progressive uremia returned despite a rising urinary output. Three days after dialysis, when the blood urea nitrogen was 153 mg. per 100 ml. and the carbon dioxide combining power 17.6 milliequiv. per liter, convulsive seizures again developed, with flaccid right-sided paralysis and respiratory standstill. Despite repeated heroic attempts to maintain life, she died sixteen days post partum and thirteen days after transfer.

Autopsy findings were hemoglobinuric nephrosis, bilateral pulmonary edema and cerebral hemorrhage.

This case was classified as a preventable death caused by reaction from an incompatible blood transfusion. Contributing causes were hemorrhage, cesarean section and placenta praevia. The ultimate result of the transfusion reaction was hemoglobinuric nephrosis, pulmonary edema, cerebral hemorrhage and uremia.

This death seems especially tragic since the patient's fate hinged upon one salient feature — namely, an error in determination of the Rh factor. This tragedy is the more poignant since she must have been first admitted to the hospital in a state of acute emergency and experienced hemorrhage, which well might have caused her death immediately. However, owing to prompt and energetic treatment, she was dramatically saved from this fate in a small rural hospital. This is in keeping with the finest traditions of medicine practiced under great difficulty. It is unfortunate that the appearance of the erythroblastotic fetus did not sufficiently arouse suspicions to make a demand for Rh-negative blood regardless of the report from the laboratory, especially since the state laboratory had once reported the blood as Rh negative. Since she had been given incompatible blood the year before, the ideal situation for hypersensitivity existed, and it is not surprising that intravascular hemolysis of the same donor's blood resulted. From here on, the story is one of unremitting effort to rectify the results of this fatal error.

"Preventable" cases are customarily subclassified for responsibility. This one has been assigned to both the laboratory and the physician. Honest errors are made by all. If the typing serums used locally were either old, ineffectual or too weak, severe criticism of the laboratory and the hospital is warranted. Even with the best serum and equipment, errors are frequent enough, and certainly only the best should be used. On the other hand, there was a known discrepancy in reports of the Rh factor, there was the appearance of an erythroblastotic infant, and there was the possibility of hypersensitivity from previous transfusion. Under these circumstances, it seems only honest and fair that the responsible physician should share with the laboratory some of the onus for the mistake.

JOHN FIGGIS JEWETT, M.D.
Chairman

WOMAN'S AUXILIARY

The following information on medical technology has been prepared for publication by Mrs. J. V. Chatigny.

One of the many rewarding opportunities for those choosing a career in medicine and science is found in medical technology. After two years of college including courses in biology and chemistry (four years are better) a student devotes a year to clinical training in an approved school of medical technology endorsed by the American Medical Association. There are over 20 of these schools in Massachusetts, mostly in hospitals, and many offer free tuition and aid. After completing the training qualified students become registered medical technologists certified by the Registry of Medical Technologists. The duties performed by technologists are too well known by physicians to need elaboration.

About two thirds of all technologists work in hospital laboratories, although many are employed in doctors' private laboratories, clinics and public-health agencies and in research. Salaries range from $250 to $400 a month. One's own demonstration on the job establishes the compensation and value of the individual.

If one has not had a college education there is a type of certificate given by the Board of Registry in histologic technic. Only a high-school education and a year of medical laboratory training are required before the student is qualified to prepare tissues for microscopical analysis.

Further information may be obtained from the

Registry of Medical Technologists, Muncie, Indiana. There are 21,000 registered medical technologists today, and by 1960 probably 50,000 will be needed.

CORRESPONDENCE

WHITHER "CAPTAIN STAPHYLOCOCCUS"?

To the Editor: Our only alternative in the losing battle with "Captain Staphylococcus" is to concentrate on the host, his environment and protective mechanisms. Chemotherapeutics and antibiotics have profoundly modified pathology and medicine, but they have done so by replacing natural recovery with an artificial one. Antibiotics limit the specific immunization reaction because of their bacteriostatic or bactericidal action directly upon susceptible micro-organisms; they actually depress the nonspecific immunity process, and do not enhance the natural resistance and recuperative powers of the patient. The emergence of resistant strains of the hemolytic *Staphylococcus aureus (Micrococcus pyogenes* var. *aureus)* to one after the other of the antibiotics shows that the answer to their conquest is not the development of more and more antibiotics, or combinations of them, but a fresh, fundamental approach to a solution to this world-wide problem. Under controlled experimental conditions, bacteriophages have been shown to be protective and curative in vivo.

The *Laryngoscope* (66:846-858, 1956) contains an article entitled "Staphylococcus Bacteriophage Lysate Aerosol Therapy of Sinusitis." This is a summation of ten years' experience in the use of a prepotent biologic that has proved to be both safe and effective; over one and a half million doses have been given, without serious side reactions. The lysates are of special value in the treatment of sinusitis, bronchial asthma and skin or mucous-membrane and wound infections, and are a specific aid in the control of staphylococcal enterocolitis, which is so prevalent owing to the indiscriminate use of the broad-spectrum antibiotics. Pyogenic micrococcal infections, crossinfections and superinfections in acute or chronic debilitating disease and surgical sepsis are playing an increasingly prominent part in the management of such conditions. Bacteriophages are one of the body's natural defense agencies. Other descriptions of the subject are given in *The Dynamics of Virus and Rickettsial Infections* (New York: Blakiston Company, 1954) and *Principles of Bacteriology and Immunity* (fourth edition, revised by Wilson and Miles, Vol. 1 and 2, Baltimore: Williams and Wilkins, 1955).

The rationale of nasal aerosol lysate therapy involves bacteriolysis in the anterior nares, the main reservoir of pathogenic staphylococci; the action of potent, highly polyvalent, type-specific, whole-culture vaccine on absorption through the nasal mucous membranes, with stimulation of local and systemic immunity and positive antibody production; increase in the opsonic index or susceptibility to phagocytosis; gradual desensitization to bacterial protein and toxins, a major consideration in the treatment of bacterial allergy, which is found in most cases of chronic sinusitis, bronchial asthma and many other chronic, enervating illnesses often complicated by ubiquitous staphylococcal infections; no development of an active opposition to the lytic effect of the phages from the antibiotic-resistant micrococci; and recognition of the significant synergistic action of staphylococcal toxins and spreading factors in allergies or infections due to these and to other bacteria and viruses. The host cells, from which the lysates are made, possess all the known characteristics of virulent, toxigenic *Staph. aureus:* they are coagulase and phosphatase positive, ferment mannitol and produce alpha and beta hemolysins, exotoxins and enterotoxins, polysaccharides, hyaluronidase, fibrinolysin, lipase, protease and penicillinase. These facts warrant a renewed effort in this field of endeavor, to fight the serologic supremacy of the pathogenic micrococci.

A. ERNEST MILLS, M.D.

West Medford, Massachusetts

REVOCATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held November 15, 1956, it was voted to revoke the registration of Dr. Sylvio J. Hebert, Amesbury, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held November 15, 1956, it was voted to revoke the registration of Dr. Louis Cohen, Winthrop, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEWS

Emotional Hazards in Animals and Man. By Howard S. Liddell, Ph.D. 8°, cloth, 97 pp. Springfield, Illinois: Charles C Thomas, 1956. $2.50. (Publication No. 299, *American Lecture Series.*)

Pavlov will undoubtedly be as great a figure in science as Freud. Certainly, both names will continue to reverberate through the halls of fame in the special section devoted to the latter part of the nineteenth and the early part of the twentieth century. Fortunately, in America, many of Pavlov's contributions have been repeated and extended by W. Horace Gantt, M.D., director of the Pavlovian Medical School in Baltimore. One of his outstanding students and followers, Howard S. Liddell, Ph.D., shows in a simple and readable way how much animals are like human beings in the organization and function of their nervous systems. Kipling said, "The things we learn from the yellow and black will help us along with the white." Equally true is the obvious fact a great deal can be learned from animals about human behavior. This book draws close and careful parallels. It is warm, witty, urbane and human. In this delightful monologue, which every physician might benefit from reading, Charles C Thomas has presented an informative and provocative treatise that reads like fiction but is profoundly scientific in its content and treatment.

MERRILL MOORE, M.D.

Neural Control of the Pituitary Gland. By G. W. Harris, F.R.S., Sc.D., M.D. 8°, cloth, 298 pp., with 54 illustrations. London: Edward Arnold (Publishers), Limited, 1955. $6.75. (Distributed in the United States by the William and Wilkins Company, Baltimore.)

This is the third in a series of monographs written under the auspices of the Physiological Society with the express purpose of providing a useful book for the advanced student of physiology. It is based on a series of lectures delivered by the author at Cambridge University. The book is broad in scope and critically reviews work on the anatomy of the pituitary gland and hypothalamus as well as the studies of the secretion of the known anterior and posterior pituitary hormones and their relations to central-nervous-system activity. In addition there are chapters on the transplantation of endocrine glands, the maturation of physiologic mechanisms involved in hormone secretion and the relation between hormones and behavior. Professor Harris, a noted and respected contributor to this field, has made available his incomparable experience not only by critically reviewing the pertinent studies but also by synthesizing them into a well written and enjoyable volume. Many photographs and clear diagrams illustrate important material and aid in the understanding of the concepts presented. The studies that are

the subject of this review clearly show the importance of the central nervous system and particularly the hypothalamus in influencing the physiology and behavior of the organism through the endocrine glands. The clinical implications of these studies, although not discussed at length by the author, are quite apparent and of utmost importance to all physicians. The book is required reading for students and investigators in related fields and is to be highly recommended to physicians interested in the physiology of behavior.

GEORGE W. THORN, M.D.

"Controlled Hypotension" in Anesthesia and Surgery. By David M. Little, Jr., M.D. 8°, cloth, 159 pp., with 14 illustrations and 18 tables. Springfield, Illinois: Charles C Thomas, 1956. $4.50. (Publication No. 283, *American Lecture Series.*)

The justification for this publication can only be based upon the findings of Hampton and Little, who stated that an over-all mortality of 1:291 occurred in patients subjected to controlled hypotension anesthesia during surgery.

The author's discussion of the physiologic changes that occur during induced hypotension is very general. Some of the statements concerning the mechanisms and causes of bleeding during surgery are evidently based upon opinion rather than upon sound investigation — for example, "venous ooze increases during surgery when 'assisted' or 'controlled anesthesia' is employed."

The chapters describing the fatal and nonfatal complications and contradictions to the use of this method warrant reading. One of the concluding statements of these chapters, "There are grave dangers associated with its use," describes the value of induced hypotension during surgery.

This monograph may be of interest to the surgeon or anesthetist who is inclined to try controlled hypotension during surgery.

BENJAMIN E. ETSTEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

British Obstetric and Gynecological Practice. Obstetrics. Edited by Sir Eardley Holland, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G., consulting obstetric and gynecologic surgeon, London Hospital, London. 4°, cloth, 1166 pp. Philadelphia: F. A. Davis Company, 1955. $29.50.

British Obstetric and Gynecological Practice. Gynecology. Edited by Aleck Bourne, M.A., M.B., B.Ch. (Cantab.), F.R.C.S., F.R.C.O.G., consulting gynecologist, St. Mary's Hospital; consulting obstetric surgeon, Queen Charlotte's Hospital; consulting surgeon, Samaritan Hospital for Women, London. 4°, cloth, 841 pp. Philadelphia: F. A. Davis Company, 1955. $29.50.

Nerve Impulse: Transactions of the fifth conference, September 20, 21 and 22, 1954, Princeton, New Jersey. Edited by David Nachmansohn, M.D., professor of biochemistry, Columbia University College of Physicians and Surgeons; and H. Houston Merritt, M.D., professor of neurology, Columbia University College of Physicians and Surgeons. 8°, cloth, 256 pp., with 82 illustrations and 2 tables. New York: Josiah Macy, Jr., Foundation, 1956. $4.50.

Group Processes: Transactions of the second conference, October 9, 10, 11, and 12, 1955, Princeton, New Jersey. Edited by Bertram Schaffner, M.D., university seminar on communications, Columbia University. 8°, cloth, 255 pp., with 23 illustrations. New York: Josiah Macy, Jr., Foundation, 1956. $3.50.

Die Behandlung des Bluthochdruckes. By Prof. Dr. L. Hantschmann, director and head, Innere Abteilung der Städt, Krankenanstalten Remscheid. 8°, paper, 92 pp., with 9 illustrations and 4 tables. Stuttgart: Georg Thieme, 1956. DM 12.- $2.85. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Clinical Pathology: Application and interpretation. By Benjamin B. Wells, M.D., Ph.D., director of clinical investigation, Lynn Clinic, Detroit. Second edition. 8°, cloth, 488 pp., with 25 illustrations and 32 tables. Philadelphia: W. B. Saunders Company, 1956. $8.50.

The Training of Sanitary Engineers: Schools and programmes in Europe and in the United States. By Milivoj Petrik, Ing., M.S., professor of sanitary engineering, University of Zagreb, and consultant in sanitary engineering, World Health Organization. 8°, cloth, 151 pp., with 8 tables. Geneva: World Health Organization, 1956. £1, Sw. fr. 12.-, $4.00. (French edition in preparation.) (Distributed in the United States by Columbia University Press, New York City.)

Silent Spokesman: An aid to the speechless. By Wayland W. Lessing. 4°, paper, 36 pp., with illustrations. Chicago: Hospital Topics, 1956. $1.50.

NONCLINICAL NOTES

YALE PROFESSOR

Dr. Lytt I. Gardner, a graduate of Harvard Medical School in the class of 1943 and a former resident and clinical research fellow at the Massachusetts General Hospital, has been appointed professor of pediatrics at Yale University School of Medicine.

NOTICES

JEWISH MEMORIAL HOSPITAL

A symposium entitled "Cerebrovascular Accidents" will be presented at a medical-staff meeting of the Jewish Memorial Hospital, on Wednesday, December 9, at 8 p.m.

Dr. Arnold Starr will discuss the traumatic, and Dr. Isadore Green the nontraumatic aspects.

YALE UNIVERSITY SCHOOL OF MEDICINE

Yale University School of Medicine announces that a lecture will be given at the Fitkin Amphitheater, on Monday, February 4, at 8:15 p.m.

Dr. Virginia Apgar will speak on the subject "Cardiopulmonary Changes at Birth."

All interested physicians are invited to attend.

LOS ANGELES RADIOLOGICAL SOCIETY

The ninth annual Mid-Winter Radiological Conference of the Los Angeles Radiological Society will be held at the Biltmore Hotel, Los Angeles, California, on Saturday and Sunday, February 23 and 24, 1957.

The conference fee of $20.00 will include two luncheon meetings featuring questions and answers. A banquet ($7.50 per plate), preceded by cocktails, will be held on Saturday evening. Reservations may be obtained from Dr. Louis J. Bonann, 1245 Glendon Avenue, Los Angeles 24, California. Hotel reservations should be made through the Convention Manager, Biltmore Hotel, Los Angeles, California.

Courtesy cards will be available to residents in radiology and radiologists in the armed forces by advance registration, with reduced tariff for the luncheon and banquet.

Dr. Merrill C. Sosman, Boston, will be among the guest speakers.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
DECEMBER 14 and 15. Bahamas Medical Conference. Page 923, issue of November 8.
DECEMBER 15. International Academy of Proctology. Page 1017, issue of November 22.
DECEMBER 18. Boston City Hospital House Officers' Association. Page 875, issue of November 1.
DECEMBER 19. American College of Chest Physicians and Overholt Thoracic Clinic. Page 1109, issue of December 6.
JANUARY 16–19, 1957. International Fertility Association. Page 1109, issue of December 6.
JANUARY 17, 1957. Arthritis Study Unit. Page 831, issue of October 25.
FEBRUARY 4, 1957. Yale University School of Medicine. Page 1163.
APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 20

THURSDAY, DECEMBER 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
8:00–9:00 a.m. Medical Journal Club. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Yamins A, Beth Israel Hospital.
*9:00 a.m. Neurological Rounds. Dr. Kane. Evans 2 Conference Room, Massachusetts Memorial Hospitals.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*10:15 a.m.–12:00 m. Medical Grand Rounds. Dr. Keefer. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00–a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:30 p.m. Gastroenterology Conference. Dr. Ingelfinger. Massachusetts Memorial Hospitals.

FRIDAY, DECEMBER 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11.15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*11:30 a.m. Tumor Clinic. Drs. Soutter and Lemon. Robinson 4, Massachusetts Memorial Hospitals.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill C. Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, DECEMBER 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*9:30 a.m.–12:00 m. Grand Rounds. Haynes Memorial Hospital, Brookline.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, DECEMBER 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Staff Meeting. Obstetrical and Gynecological. Drs. Abrams and Parker. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesiology Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, DECEMBER 25

Holiday

WEDNESDAY, DECEMBER 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Dr. Smithwick. Evans 8 Amphitheater, Massachusetts Memorial Hospitals.
*10:00 a.m. Ward Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Pulmonary Tuberculosis. Dr. Robert H. Hermanson. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m. p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Krause. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*1:00–2:00 p.m. Surgical Staff Meeting. Dr. Smithwick. Evans Conference Room, Massachusetts Memorial Hospitals.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00 p.m. Vascular Rounds. Robinson 4, Massachusetts Memorial Hospitals.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*Open to the medical profession.